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PAUL W. CLOUGH

Assistant Editor

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NUMBER 1

THE PATHOGENESIS OF LUPUS ERYTHEMATOSUS AND ALLIED CONDITIONS *

By PAUL KLEMPERER, M.D., *New York, N. Y.*

IN 1872 when Kaposi¹ published his first report of acute lupus erythematosus, medicine was still dominated by the pathologic-anatomic doctrine that disease is the result of alterations of bodily structure. Today the study of pathogenesis aims at a full comprehension and integration of all the factors of the external and internal environment which bring about that altered state of life, called disease. Inquiry into the genesis of a disease can no longer be content with the mere perception of structural alterations. Yet the definition of most maladies still depends upon an exact knowledge of characteristic organ and tissue changes. Therefore, the student of pathologic anatomy can still make his worthwhile contribution to pathogenesis. The history of our knowledge of acute lupus erythematosus readily supports the thesis that anatomic pathology can clarify *some* problems of a puzzling disease and might be able to guide an inquiry into its fundamental nature.

Kaposi's original description of acute lupus erythematosus referred to some of the extracutaneous symptoms of the disease. Subsequent dermatologic investigators added further observations, which were well summarized by Jadassohn² at the turn of the century. Nevertheless it was generally accepted that acute lupus erythematosus was merely a cutaneous disease. The general constitutional symptoms such as fever, prostration, typhoid state, as well as the local morbid phenomena such as joint pain and swelling, ulcerations of mucous membranes, glandular swelling and albuminuria were vaguely interpreted as the manifestations of a severe "toxic" state induced by the severe involvement of the skin. Autopsy reports of this period mentioned the occurrence of pneumonia and pleuritis, parenchymatous nephritis, occasionally tuberculosis and degeneration of the parenchymatous

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From the Laboratories, Division of Pathology, The Mount Sinai Hospital, New York, N. Y.

organs. Pernet³ referred to small vegetations on the mitral valve in his case. In the question of etiology, main emphasis was placed upon the rôle of tuberculosis. Indeed, up to recent years the tuberculous etiology of acute lupus erythematosus has been seriously considered; finally it was disproved by Keil.⁴ During the first two decades of this century, an increasing number of well observed cases was reported by competent clinicians from the broader viewpoint of internal medicine (Goeckerman,⁵ Keefer and Felty⁶). Acute lupus erythematosus thus came to be recognized as a clinical entity in which the cutaneous lesions were merely part of a serious systemic malady. However, attempts to define the disease in terms of morbid anatomy were less successful because the observations at autopsy were not characteristic and mostly disclosed only the terminating events of a grave systemic disorder. Libman and Sacks'⁷ report of an unusual form of endocarditis in cases with the characteristic clinical symptom complex constitutes the first significant contribution to the comprehension of the morbid anatomy of acute lupus erythematosus. Subsequently these observations were confirmed and amplified by Gross (1932⁸ and 1940⁹). These disclosures indicated that lupus erythematosus should be defined anatomically as a primary cardiac disease. In 1935, Baehr, Klemperer and Schiffrin¹⁰ called attention to conspicuous and widespread lesions of blood vessels and to frequent involvement of serous membranes. We then tried to correlate the clinical symptoms with these structural alterations. We maintained that the co-existing endocardial, vascular, serosal and joint involvement must be the manifestation of a primary injury of the endothelial cells and that acute lupus erythematosus could be explained as the result of the action of an endotheliotropic injurious factor. Within the following years similar observations were reported by Jarcho,¹¹ Denzer and Blumenthal,¹² and Rose and Pillsbury.¹³ Ginzler and Fox¹⁴ added lymph node necrosis to the anatomic findings. The report of Rakow and Taylor¹⁵ deserved special mention because it concerned a patient with the characteristic clinical symptoms of acute lupus erythematosus but without any cutaneous manifestations. Characteristic vascular lesions were found within the lungs and kidneys.

Other authors dissented. Some asserted that on the one hand they could not recognize identical lesions in a considerable percentage of their cases, and on the other hand others believed that the histologic alterations reported by us were not characteristic but could be found in other toxic diseases.¹⁶ This criticism called for further study. A series of 12 new cases afforded the opportunity. Microscopic examination revealed not only vascular lesions but other tissue alterations which had not been noticed previously. Restudy of the old material disclosed that identical changes had been present but had eluded our attention. These histologic findings were fully described and illustrated by us in 1941,¹⁷ and a detailed account can therefore be omitted.

Our microscopic observations showed the presence of a widespread alteration of the connective tissue, affecting the heart, serous membranes,

vasculature, lymph nodes, skin and mediastinal and retroperitoneal area. In two recent observations the capsule of the shoulder joint showed identical involvement (figure 1). The morbid process becomes manifest in focal fibrinoid metamorphosis of the collagenous fibers resulting occasionally in fragmentation of these elements, and in swelling and increased density of the interfibrillar homogeneous ground substance which normally is almost invisible. Such foci are more or less heavily infiltrated by polymorphonuclear leukocytes and lymphocytes. The fixed connective tissue cells, fibroblasts and histiocytes, while increased in number, almost invariably show evidence of decay such as pyknosis and nuclear fragmentation. The behavior of the

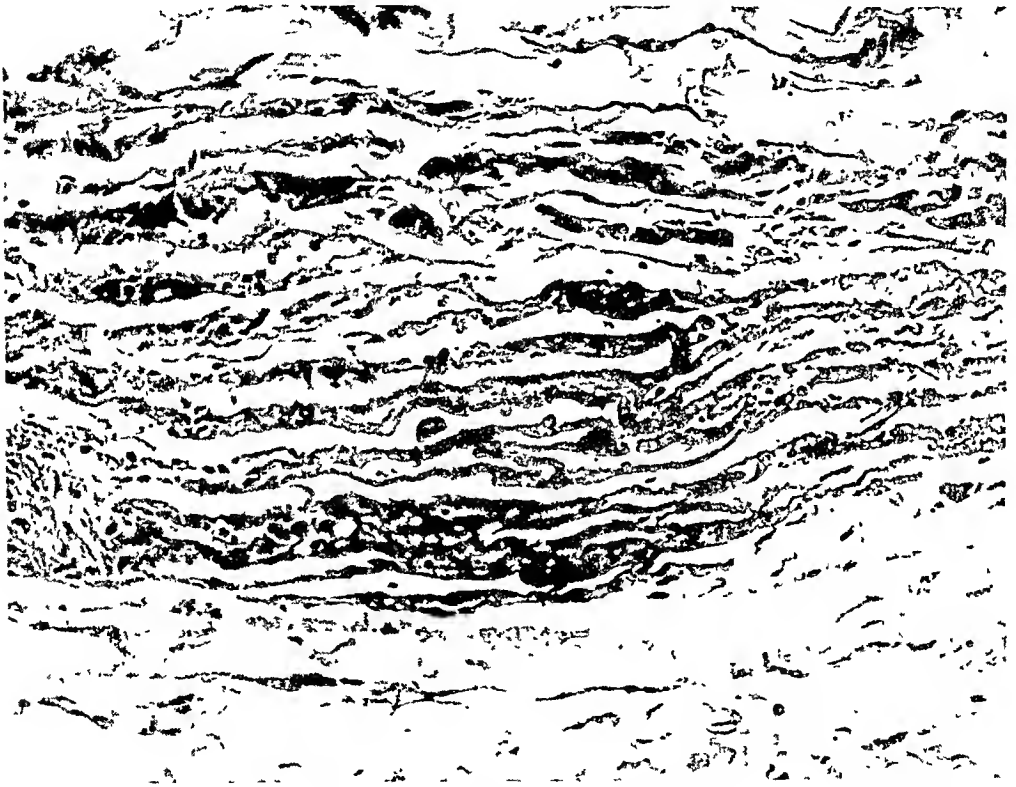


FIG. 1. Capsule of shoulder joint showing thick and eosinophilic collagen fibers, which gave staining reaction like fibrin.

cells in the injured portions of the cardiac connective tissue permits of a differentiation from the injury in rheumatic fever in which fibrinoid alteration is also evident. In rheumatic fever the histiocytes show conspicuous and sustained proliferation, which leads to the formation of the characteristic Aschoff cells. Such cells are absent from the heart in acute lupus erythematosus. The arterial lesions of lupus erythematosus which are predicated upon an injury of the connective tissue framework of the vessel are associated with a mild perivascular cell infiltration. This contrasts with the striking perivascular cell infiltration and proliferation of periarteritis nodosa in which, however, fibrinoid alteration also plays a significant rôle. The alteration of

the glomerular capillaries (wire loops and focal necrosis), so conspicuous in acute lupus erythematosus, has been observed neither in rheumatic fever nor in periarteritis nodosa. Another microscopic feature present with conspicuous frequency in acute lupus erythematosus but not observed in rheumatic fever and periarteritis nodosa is sclerosis of collagen fibers around the follicular arteries of the spleen. This lesion also reflects a fundamental alteration of the connective tissue though of a nature different from fibrinoid metamorphosis. In a review of 20 cases of acute lupus erythematosus we observed the alterations here referred to with such frequency (table 1) that

TABLE I
Collagen Alterations Observed in 20 Consecutive Cases
of Acute Lupus Erythematosus

Pericarditis	14 or 70%
7 or 35% showed conspicuous collagen changes	
Heart	
Endocardium	11 or 55%
Myocardium	7 or 35%
Kidney	
"Wire loop" changes	12 or 60%
Focal loop necrosis	17 or 85%
Vascular lesions	8 or 40%
Vessels and other sites	13 or 65%
Spleen	19 or 95%

we felt justified in inferring that they were significant. Because the structural alterations are primarily localized within the extracellular portions of the connective tissue (fibers and ground substance) they cannot be classified according to the conventional principles of cellular pathology, as degenerative or inflammatory. But it is apparent that they are the manifestations of an essential change in the physico-chemical state of these connective tissue elements. This point of view applies, of course, to all the phenomena with which anatomic pathology is concerned. But it is of greater significance for the comprehension of abnormal states of the connective tissues. The association of morbid conditions of cells with visible alterations of structure has been under investigation for nearly a century. These studies have been facilitated by the clear definition of the two constituents of the cells, the nuclei and the cytoplasm. The series of structural alterations which denote an altered state of life of the cell until its ultimate death is well known. In contrast, the intercellular substances, and especially the homogeneous ground substance of the connective tissues, have received much less attention. The microscopic definition of the latter has been made most difficult because conventional methods of histologic preparation render it poorly visible. Therefore, it is reasonable to assume that only certain profound alterations of its physical and chemical constitution become evident upon microscopic examination. This premise is illustrated by the experience that in total scurvy the fundamental disturbance of the intercellular substances is not directly visible. It seems, therefore, not too speculative to believe that significant

alterations of the intercellular substances may exist in other maladies although they cannot be recognized with the available histologic methods. This hypothesis may explain the absence of striking microscopic lesions in some of the cases of acute lupus erythematosus. It also should stimulate investigations with other methods than those of conventional histologic technique, attention being paid especially to alterations of the connective tissue which might easily be neglected because of their apparently trivial character. In two recent cases I was impressed by a striking widening of the myocardial septa which could have been interpreted as mere edema (figure 2A). However, the application of mucus stains (toluidine blue) revealed intense metachromasia, which indicated the conspicuous presence of mucoproteins within the intercellular ground substance. This was associated with only a minimal fibrinoid alteration of the collagen fibers (figure 2B). I believe that the present state of information permits us to conclude that acute lupus erythematosus is defined anatomically as a disease characterized by a fundamental alteration of the collagenous portions of the connective tissue. The exact nature of this alteration must be determined by investigation with the methods of histology, biochemistry and biophysics.

Generalized scleroderma, like acute lupus erythematosus, was originally regarded as a primary cutaneous disease. Histologic examination revealed a conspicuous thickening and homogenization of the connective tissue of the corium. Similar sclerosis was soon observed within the vessels of the skin and in those of the internal organs. Subsequent pathologic investigation disclosed a sclerotic involvement of the alimentary tract, lungs, heart and skeletal muscle. This sclerotic process can be traced to the connective tissue framework of these organs and appears to be the result of an increase in fiber formation. This may or may not be accompanied by proliferation of fibroblasts. In association with this progressive sclerotic transformation of the collagenous elements, fibrinoid alterations were observed by several authors (Masugi and Ya-Shu,¹⁸ Pollack,¹⁹ Bevans²⁰). The lesions showed some similarity with those occurring in acute lupus erythematosus. Since sclerosing collagen alterations occur in the spleen of acute lupus erythematosus it may be inferred that fibrinoid metamorphosis and sclerosis represent different phases of a disturbed chemico-physical state of the collagenous tissue. Certainly the morphologic evidence permits the conclusion that generalized scleroderma is likewise characterized anatomically by a fundamental implication of collagenous tissues.

The observations previously summarized indicate that acute lupus erythematosus shares a common element with generalized scleroderma, rheumatic fever, and even periarteritis nodosa in the systemic involvement of the collagenous tissue. This similarity might be interpreted as implying that all these diseases are closely related pathogenetically. In my opinion such an inference is unwarranted.



FIG. 2A (*above*). Myocardium showing widened septa with conspicuous interfibrillar ground substance which showed metachromasia with toluidine blue; this is indicative of the presence of mucoproteins.

FIG. 2B (*below*). Same case. Myocardial septum showing fibrinoid alteration of collagen fibers.

Structural alterations are the manifestations of a reaction to injury. Since the modes of reaction of which a tissue is capable are not unlimited, different injuries may provoke similar responses. The question, then, arises what conclusions, if any, can be drawn from morphologic investigations as to the etiology of acute lupus erythematosus.

Painstaking bacteriologic examinations during the life of the patients and of the tissues after death have failed to disclose bacteria as the immediate cause of the disease. Yet the acute or subacute febrile course and the severe toxic symptoms still suggested an infectious process. Hypersensitivity to bacteria or bacterial products was, therefore, proposed as a probable cause (Stokes²¹). This hypothesis is strengthened by the fact that fibrinoid collagen changes have been found as a conspicuous feature of the morbid anatomy of acute lupus erythematosus (Fox,²² Theilum²³). The occurrence of similar changes in generalized scleroderma has persuaded Masugi and Ya-Shu to assume that this disease is likewise of allergic origin. It is generally accepted that fibrinoid collagen alterations occur in allergy. This was first demonstrated by Gerlach²⁴ and Klinge²⁵ in animal experiments. Its occurrence in diseases with an obvious allergic background such as periarteritis nodosa (Gruber²⁶) and serum sickness (Clark and Kaplan²⁷), and in drug hypersensitivity (Rich^{28,29}) supply further evidence for a pathogenetic relationship. The allergic hypothesis of the etiology of rheumatic fever, while not yet fully proved, certainly deserves serious consideration. Yet we must not lose sight of the fact that collagen alterations hardly distinguishable microscopically from those seen in allergy can be observed in situations which bear no relation to hypersensitivity. It has long been known that fibrinoid collagen alterations occur in a variety of acute bacterial infections; this fact has been stressed even by Schosnig,³⁰ a student of Klinge, the most ardent advocate of the significance of collagen alterations in allergy. Identical changes can be observed in inflammations due to chemical or physical irritation (figure 3A). In experimental hypertension, conspicuous vascular lesions simulating periarteritis nodosa have been reported repeatedly (figure 3B). The alteration which is so often found in collagen fibers in the base of a peptic ulcer or in the vicinity of acute pancreatic necrosis is strikingly similar to fibrinoid collagen changes. Finally Wu Tsai Tong³¹ showed that simple squeezing of the skin of rats results in collagen alterations indistinguishable from fibrinoid changes. Routine material received in the laboratory of surgical pathology, especially needle biopsies, frequently shows the effect of such undue compression. These observations seem to justify the general conclusion that fibrinoid collagen alteration must not be interpreted solely and invariably as an expression of hypersensitivity. Consequently, I hesitate to accept the doctrine that any disease anatomically characterized by such connective tissue lesions is presumably of allergic origin. Obviously, if observations during the life of the patient so clearly reveal allergic manifestations as in serum sickness and periarteritis nodosa stubborn

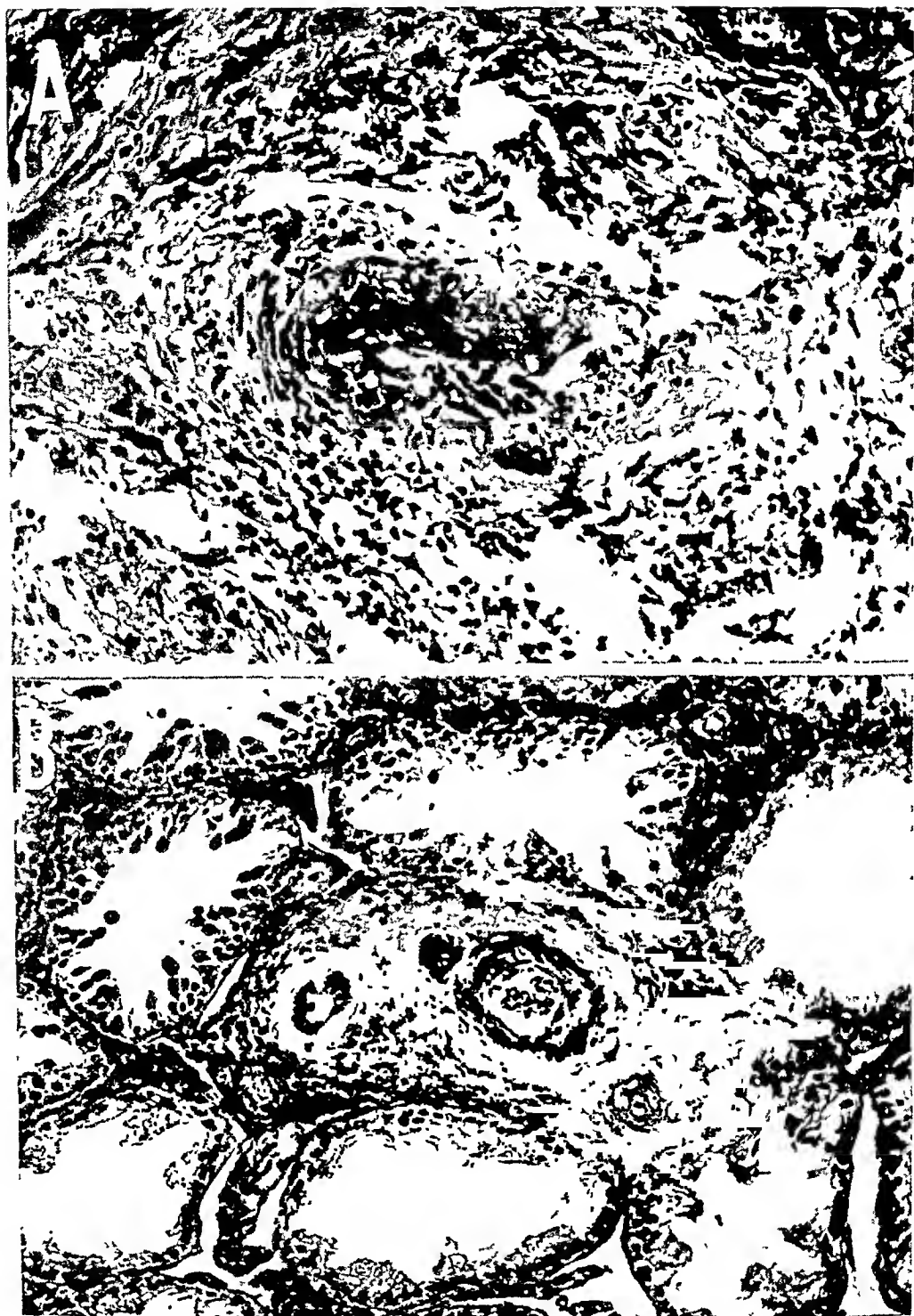


FIG. 3A (*above*). A small artery in the base of a cutaneous ulceration due to roentgen-ray burn showing segmental fibrinoid alteration with necrosis.

FIG. 3B (*below*). Testis of rat with experimentally produced hypertension showing small arterioles with fibrinoid alteration of the wall.

skepticism would be unsound. But there is no direct clinical evidence in support of hypersensitivity in acute lupus erythematosus and in generalized scleroderma (Baehr and Pollack³²). An allergic hypothesis rests, therefore, upon the histologic features alone and it must be stressed that these anatomic facts have not yet been analyzed sufficiently to permit of a final pathogenetic synthesis.

At this juncture it may well be asked whether and in what way further studies in anatomical pathology can contribute to a clarification of the pathogenesis of acute lupus erythematosus and allied conditions.

The mere perception and description of structural alterations can no longer be the ultimate aim of anatomic investigation. Effort must be directed toward a comprehension of the chemical and physical state which is responsible for the altered microscopic appearance. This aim of anatomic pathology in general is still far distant.

The morbid process of acute lupus erythematosus and scleroderma affects the collagenous tissue system of the body in a conspicuous manner, but we cannot comprehend its nature, because even the normal structure of this matrix is still incompletely understood. Examination of the connective tissue fibers with the aid of the electron microscope and roentgen-ray diffraction have disclosed their molecular structure (Schmitt³³); but very little is known of altered collagen fibers. In particular, the fibrinoid metamorphosis which is so conspicuous in acute lupus erythematosus and allied conditions requires more adequate definition. It has not yet been ascertained whether the peculiar appearance of the collagen fiber is due to a material alteration or merely to impregnation with true fibrin or possibly the result of a combination of both factors. Attention has already been called to the fact that fibrinoid collagen changes occur in various unrelated conditions. The conventional methods of histopathology can not establish with certainty that the microscopic similarity reflects an actual identity of the chemical and physical constitution of the affected fibers.

Microscopic evidence points to an alteration of the homogeneous ground substance as a significant feature of the morbid process in acute lupus erythematosus and generalized scleroderma. But the nature of the homogeneous ground substance, its relation to the fibroblasts and to the connective tissue fibers still awaits fuller comprehension. Old and recent observations indicate that the ground substance is composed of a variety of mucoproteins. It is known that its colloidal state is affected by enzymes, such as hyaluronidase (K. Meyer³⁴). Various female sex hormones seem to exert an opposite influence (Sprunt et al.³⁵). By repeated injections of estrogen Leo Loeb and associates³⁶ produced hyaline changes in the stroma of various organs, while Selye³⁷ provoked strikingly mucinous edema of the skin in hairless mice by the repeated application of estradiol. The influence of ascorbic acid upon the ground substance and its relation to collagen fiber formation has been ascertained by Wolbach and Howe³⁸ and Wolbach.³⁹ Such fragmentary

observations must be expanded and united. By purposeful experimental studies we must try to identify structural alterations of the connective tissue in terms of reactions to well defined chemical and physical influences. Only upon such basic investigations can a successful inquiry be established into the cause of such puzzling diseases as acute lupus erythematosus, generalized scleroderma and allied conditions.

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THE CARDIAC LESIONS OF ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS *

By ELEANOR M. HUMPHREYS, *Chicago, Illinois*

ACUTE disseminated lupus erythematosus is a disease of unknown etiology and of polyphasic symptomatology which quite frequently affects the heart. Views are conflicting as to its true nature, and as to the pathogenesis of its focal lesions. Despite the polymorphism of its lesions, it is possible to recognize certain common and even highly characteristic features, clinical and pathological. It may at first seem unreasonable to group for analysis cases with and cases without the typical cutaneous eruption of acute lupus erythematosus. Although we have long been used to thinking of rheumatic fever without rheumatic joints, we are only now learning that other members of this group of diseases which affect the connective tissues, lupus erythematosus, dermatomyositis and scleroderma, may exist without their classical dermatologic manifestations.

From many studies of cases of acute systemic lupus erythematosus it is clear that there is great variability in the early symptoms and that arthritis, pleuritis and other less well defined complaints may long precede the appearance of the typical erythemas. The group of 21 cases forming the basis for this report includes 15 patients who had, while under observation, lesions considered to be typical. Four others described eruptions which were at least suggestive, and in two patients there was no story of cutaneous involvement. The group shows the usual predominance of females, with 17 between 19 and 39 years of age and two above 50. Of the older females, one, aged 52 years, had a typical facial eruption, as well as pathognomonic endocardial lesions. The oldest patient, a woman of 55 years, had some atypical symptoms but her acute generalized eruption was identified clinically and by biopsy as acute lupus erythematosus. Each of the two men in the group was 52 years old—a somewhat higher age than in most of the reported cases among males. One had a typical facial “butterfly” as well as erythematous patches on the extremities. The clinical course was brief, ending with pneumonic complications. The other male had no recognizable cutaneous eruption, but a classical endocarditis of the Libman-Sacks type found at autopsy was considered adequate to establish the diagnosis.

All 21 patients at one time or another had complained of malaise and weakness, of pains in the joints and muscles, of pleurisy, and of vague abdominal distress. Anemia, and leukopenia (except at times of infectious complications) were invariably present. The same was true of tachycardia. At some period every patient had pulse rates above 100 per minute. Rates between 120 and 140 were noted frequently, and values of 160 to 180 were

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From the University of Chicago, Chicago, Illinois.

noted occasionally. Symptoms of local vasomotor disturbances were sometimes conspicuous. Some patients complained of retrosternal distress. Others had severe upper abdominal pains with nausea and vomiting. In the late stages the course was often dominated by the signs and symptoms of failing renal function associated with glomerulonephritis; of diffuse or focalized cerebral disease; of pulmonary disease. Obviously with the preterminal development of decubitus ulcers, of abscesses, of buccal or esophageal or intestinal erosions, bacterial infections frequently complicated the final stages. It is highly probable, too, that therapeutic measures sometimes modified the terminal course, and the character of lesions. One other group of clinical manifestations must be taken into account in any analysis of cardiac status. These are the effects of general debility, often verging on cachexia. These patients frequently suffered from severe anorexia, and many of them lost 20 to 30 per cent of their body weight. The low plasma albumins and low A/G ratios of most of these patients should be noted, as well as the increased globulin levels. Apparently false-positive Wassermann or Kahn tests were observed in at least 10 of the 21 cases.

It is not necessary to discuss in detail the characteristic valvular and mural non-bacterial vegetations, first reported by Libman and Sacks¹ and since described and pictured by many others.^{2, 3, 4} It might be well to stress that they may be far from obvious, if they are flat spreading lesions on valve surfaces, or if they are hidden away, beneath the cusps, or in the deeper niches between muscular trabeculae. They may be found on any of the four valves, or in any chamber. Endocardial lesions were found in 12 of our 21 cases, and were hard to detect in four hearts in which they had become almost completely organized. Save for the bulkier lesions affecting two, three, or four valves (observed in seven cases) endocardial lesions were easier to recognize in microscopic sections than they were grossly.

Some focal myocarditis was encountered in most of the 21 cases. At the mildest the lesions were indistinguishable from the minor scarring of rheumatic or arteriosclerotic disease, or were indeterminate small exudative lesions of doubtful significance. Obviously these may have been unrelated to the major disease. More significant were the fine scars, like those of small infarcts; the increased density of collagen along many or most of the inter-muscular septa; the thickened small arteries. Myocardial lesions of these types, probably due in part to anoxia were found beneath the more extensive mural vegetations, or near partially or completely occluded arteries. Also there were acute exudative reactions, not easily interpreted. Fresh fibrinoid necrosis of collagen or of vessel walls was easily demonstrable in the more severe cases. In a considerable number of hearts, there was marked loosening of the fibrous substances, producing an edematous appearance not unlike that of the beri-beri heart. In several, severe fatty degeneration of myocardial fibers was noted. No active rheumatic lesions were seen.

In a number of patients, there were no changes other than interstitial edema, atrophy of fatty tissue, and the presence of dense collagen and a few

round cells near the epicardial surface. More often there was a frank pericarditis, affecting visceral and parietal pericardium and the adjacent pleura and mediastinum. In nine cases the process was serofibrinous, and in five of these (all with nephritis) there were effusions of 600 to 950 c.c. In six cases the pleural space was obliterated by loose gelatinous fibrous adhesions. There were foci of fresh necrosis, or of fibrinous and cellular exudation, within these adhesions.

The presence of adhesions or shaggy exudates as well as the edema and scarring of the walls interfered with precise estimates of cardiac weight. In proportion to the wasted state of the bodies of these patients, the cardiac weights were usually normal or increased (est. 250 to 300 gm.). In the patients who had nephritis for a sufficient period, weights of 350 to 450 gm. were observed. The larger hearts were found in patients whose nephritic symptoms had been present long enough for hypertension to develop. In one such patient the blood pressure had risen from 115 mm. Hg systolic and 75 mm. diastolic to 170/120 as the disease progressed. The blood pressures were usually normal or more often low, in the absence of renal disease.

Electrocardiographic data were available for 17 patients, with from one to three tracings per patient. While the examinations were not always made at periods of severe symptoms, there was, in general, a fair correlation with the severity of myocardial lesions. The commonest finding was lowered amplitude with evidence of minor myocardial abnormality. Arrhythmias, with extrasystoles, were observed three times. In one other case the tracing demonstrated an auricular flutter with a 2:1 ratio and a ventricular rate of 175 per minute. This tracing was made two days ante-mortem, on a young woman with severe myocardial and endocardial disease.

In conclusion, it is obvious that it is often impossible to evaluate with any precision the severity of the cardiac lesions in the patient with acute lupus erythematosus. The patient dying of this disease often presents simultaneously, symptoms related to a polyserositis, including a pericarditis; to acute or chronic renal disease; to abnormalities of the nervous system; to nutritional disturbances; to chronic and acute pulmonary disease; to acute bacterial infections. At least a few of them have had preceding rheumatic heart disease. It is obvious why so little precise information can be obtained, with the technics of physical diagnosis. Probably the best clue to the severity of cardiac injury is a series of electrocardiograms. Even this tool is subject to confusion, particularly in the presence of a pericardial effusion.

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THE PHYSICAL EXAMINATION: HELPS AND HINDRANCES *

By JAMES J. WARING, M.D., F.A.C.P., *Denver, Colorado*

"But it is by your own eyes, and your own ears and your own minds and (I may add) your own heart that you must observe and learn and profit." A. Latham. Harvey Cushing "The Life of Sir William Osler," Clarendon Press, 1925, p. 553.

THE five essentials to a good physical examination are :

1. A good light
2. A favorable position of the patient
3. A quiet environment
4. A coöperative patient
5. An experienced physician.

Without any or all of the first four even the experienced physician is under a handicap. The physician must not let the patient for his own sake even unconsciously impose conditions of the examination which may seriously interfere with the effort to obtain information necessary for diagnosis and treatment.

1. A Good Light. Because he had the rare faculty for imparting information in a memorable fashion, William Osler was a great teacher. He used with equal skill admonition, sarcasm, humor, classical allusion and even the device of stage-setting. On the occasion of a visit by Dr. Alexander Lambert of New York to the wards of the Johns Hopkins Hospital, Osler unobtrusively manoeuvred Dr. Lambert into a position between the window and the patient's bed. The stage thus set, he asked the student to present the case.

Osler : "How will you begin the examination of this patient?"

Student : "I will begin by inspecting him."

Osler : "No, Sir : Not yet. Something before that."

Student is at a complete loss.

Osler : (*putting his arm around Dr. Alexander Lambert's shoulders and pointedly drawing him out of the light*) "You would first say 'Alexander, please stand out of my light.'"

Thereupon would follow a rapid interrogation, often only by glance of those piercing eyes, to see which ones knew the ancient story of Diogenes.

* Presented at the Twenty-Eighth Annual Session of the American College of Physicians, Chicago, April 28, 1947.

The illustrations in this paper were made at my direction by Allen T. True of Denver.

The medical profession has perhaps limited itself too much to photographic illustration. A point humorously depicted might linger longer in the memory.

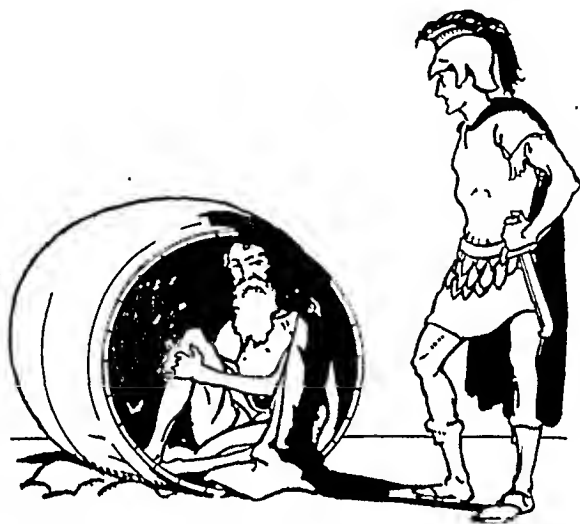
the Cynic Philosopher who lived in a tub, and Alexander the Great (figure 1).

"What can I do for you," said Alexander..

"Just stand out my light," replied Diogenes.

So runs the story. Today Diogenes would promptly reply: "Please find me an apartment, Alex! This tub has no facilities."

I believe this story has great teaching value and use it occasionally on the wards of the Colorado General Hospital to fix in the students' minds the



DIOGENES: "ALEXANDER - PLEASE STAND OUT OF MY LIGHT"

FIG. 1. The first essential to a good physical examination is to have the patient in a good light.

importance of a good light for a good examination. Practical illustrations could be multiplied.

Take just one:

For a week a student nurse had suffered from nausea, vomiting, general abdominal distress and fever. Except for a slightly tender right hypochondrium the physical examination was said to be inconsequential, the white blood count and the urinalysis were normal. The resident staff was puzzled.

I found the patient in a four bed room in a cubicle farthest removed from the window.

"Pull the bed over by the window so we can have a good look at her," was my first order. It was done.

"Why," said the surprised patient to the equally surprised staff, "I'm jaundiced!"

2. *A Favorable Position of the Patient.* I have chosen a fat Dowager (figure 2) in the middle of a huge low bed to illustrate my next point: the patient must be in a position to facilitate not obstruct the examination. All parts of the patient's body must be easily accessible to the examiner's hand and eye. This poor lady has to have a low bed because she is too heavy and unwieldy to get into a high one. A narrow bed would be dangerous because she would siphon off on to the floor if her panniculus ever started overflowing the edge of the bed. So there she lies and your problem is to find out what ails her *without breaking your back*.

Now, to get the patient in a favorable position for examination may involve nothing more than having the disrobed patient sit up or lie down. In

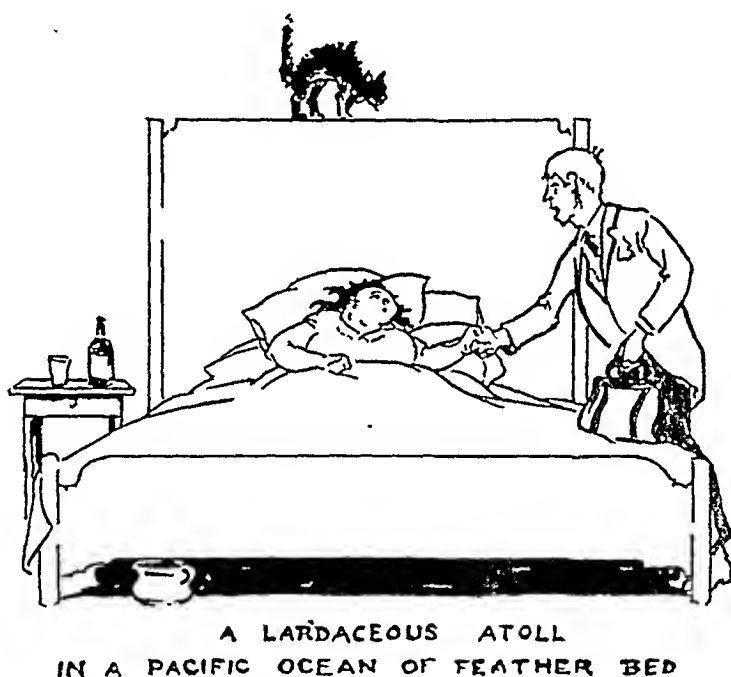


FIG. 2. The patient must be in a position to facilitate not obstruct the examination.

the case of our Dowager, there she sits in a dim light, insulated by adipose tissue, bed clothes and distance, a lardaceous atoll in a Pacific ocean of feather bed, while you circle helplessly, so to speak, three miles off-shore, wondering what the hell is going on inside the old gal!

What to do? Get the best light in the room you can; daylight is always preferable to artificial light. While someone gets the gown off and a wrapper on you consult the bath-room and run some hot water on your cold hands and the cold bell of your stethoscope!

You now go over your patient in bed systematically from head to feet, not neglecting the neurological examination and a careful appraisal of the state of the circulation in the lower extremities: Then, even though it may take

much effort, a derrick and half the neighborhood,* you get the patient out of bed and in a straight chair in a good light for further and more satisfactory examination of heart and lungs. The distortions of physical signs produced by asymmetrical positions in bed sometimes defy reliable separation from the signs of disease. A position of the body, therefore, favorable for a good examination involves first, accessibility to the examiner and secondly, symmetrical arrangement of trunk and extremities so that the two sides of the chest may be compared in all particulars.

Examination of the chest with the patient lying on the side in bed is particularly treacherous for at least four reasons: (1) The diaphragm changes asymmetrically level and amplitude of swing, (2) the curvature of the spine changes the costal relations, (3) the air in the mattress acts as a resonator to alter percussion notes, especially over the lung next the bed, (4) hypostatic moisture may be confused with the râles of a basal pneumonia.

While the patient is upright in the chair, do not fail to listen to her lungs beneath her breasts which she can lift out of your way first on one side and then on the other. Basal tuberculosis is rare but occurs often enough even in elderly people.

Among petty grievances of the examining physician I give first place to the lady of some 40 summers who keeps a determined clutch to her nightgown over her not too-curvaceous bosom as you patiently struggle to get an unobstructed "listen" to her heart and lungs.

The average woman submits with reasonable cheerfulness to exposure of her abdomen from the rib margins to the umbilicus. Below this, trespass at your peril! The stubborn clutch of the over-modest woman to the bed clothes as you push them down to the decent "symphysis-pubical" level is another annoyance. You push the covers down, she pulls them up. You somewhat fretfully push them down again and again she pulls them up. Victory in this little contest must rest with the doctor!

Arrange the bed covers yourself and, if need be, summarily dispense with the officious nurse or relative who seems to think that her mission in life is to protect the patient against indecent exposure. Every act of this miserable creature seems a pointed reminder to the physician not to let his thoughts stray from the professional job off into amorous avenues! I suspect this person annoys the patient as much as the doctor. Fortunately, their number is not great.

3. *A Quiet Environment.* A quiet environment is best obtained by prompt ejection of cats, dogs, canary birds, children and surplus relatives (figure 3). On occasion, a single member of the household may remain to supply information which for one reason or another the patient cannot give.

Suppress firmly but politely all unnecessary talking in the sick-room, whether by family, nurse, patient or colleague.

*The neighbors are always glad to help. It gives them a chance to satisfy their curiosity about our Dowager and an opportunity to meet the Doctor.

Tactfully reassure your nervous colleague who has called you in consultation. The poor fellow is so afraid you will discover something he has overlooked that he gets in your way at the bedside. His head bumps yours, as he tries to look down the patient's throat while you are looking, his hands tangle with yours on the patient's belly, his stethoscope competes with yours for a place on the patient's chest. Don't be this chap yourself and don't let your colleague get that way. Much of your success as a consultant will depend upon your skill in putting at ease early and promptly both the patient and your colleague.

One other piece of advice I consider of great importance to the family physician. Never fail to reexamine the patient again immediately before the consultant. You thus protect yourself against changes which may have taken place since your last examination. The old alibi "that is something

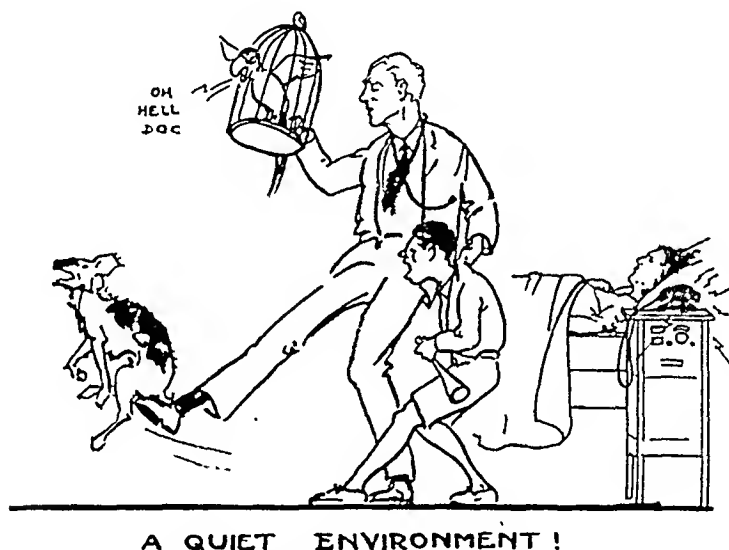


FIG. 3. A quiet environment is best obtained by prompt ejection of cats, dogs, canary birds and surplus relatives.

new" is weak! It carries no conviction to consultant, patient or watchful family.

Too often the doctor, fearful of giving offense, permits conversation in the sick-room between colleague, nurse and relatives and so impairs his examination. In teaching this point about a quiet environment, I tell the boys the story of old Dr. John Abernethy (1764-1831), a somewhat cantankerous English surgeon of great distinction as a teacher. Annoyed by the stream of chatter from the mother of a young woman he was trying to examine, he suddenly said:

"Madam! Stick out your tongue!"

Madam X (*protesting*): "But, Doctor, there's nothing wrong with me."

Dr. Abernethy (*savagely*): "Madam! Stick your tongue out."

Madam X (*red-faced, sticks her tongue out*).

Dr. Abernethy: "Now, Madam! Keep it out." (*He turns back to his examination.*)

One may legitimately assume that Madam X was thereafter *speechless*, with indignation!

In summary, while the doctor makes his examination, every distracting influence must be removed. By tact, diplomacy and force of his personality the doctor must dominate the sick-room.

4. *A Coöperative Patient.* A coöperative patient may be defined as one who submits willingly if not cheerfully to the examination, who endures real discomfort and all necessary exposures with patience and dignity, who is neither a shrinking "sissy" nor a too-impassive stoic, who responds with brevity and intelligence to interrogation, who volunteers little but enough, who knows the difference between the relevant and the irrelevant. A coöperative patient seems to know instinctively what to do and to say to help the doctor and herself and not to hinder him and herself in his examination. A coöperative spirit is in-born but can be inculcated. Some unfortunates who have seen much illness and perhaps suffered much at the hands of many doctors learn the technic of the examination and make "good patients," others never learn to submit gracefully.

But a satisfactory physical examination does not depend solely upon the patient. Two human beings are involved, the doctor and the patient. The doctor can take a shy, sick woman through a searching examination without either causing pain or wounding her pride. On the other hand, at the very outset, he can demoralize a readily coöperative patient by needless roughness and disregard of finer sensibilities.

The physical examination must be made tactfully, patiently, unhurriedly, thoroughly. Conducted in those terms, it goes a long way toward inspiring confidence and uncovering the cause of the patient's illness.

5. *An Experienced Physician.* Until now I have spoken in general terms of the physical examination. From here on, I shall speak of specific methods of examination, of the signs and symptoms of disease and their interpretation.

My colleague, Harry H. Gordon, Professor of Pediatrics at the University of Colorado School of Medicine, in a personal communication, points out that errors in pediatric physical diagnosis are easily made through failure to distinguish between negative findings and the results of an incomplete examination. For example, he says, one should distinguish between:

1. Normal discs and retinae and a fundus not seen because of crying, ocular movement or constricted pupils.
2. A normal ear-drum and one not seen because of the use of too large an ear speculum or because of obstruction of the auditory canal by wax.
3. A normal pharynx and one not seen because of regurgitated milk.
4. Normal auscultatory findings and ones obscured by the child's crying.

5. Normal abdominal findings and ones obscured by involuntary abdominal rigidity due to crying.

The importance of being sure that you have had an adequate "look," a satisfactory "feel" and an undisturbed "listen" is just as fundamental to good physical diagnosis in the adult as in the child.

Gordon also called my attention to a very practical point in the diagnosis of meningitis in an infant. The tension of the patent anterior fontanelle is a good measure of intracranial pressure and is thus of considerable aid in diagnosis. If the infant with meningitis is badly dehydrated or in circulatory collapse, the pressure of the cerebrospinal fluid will be low instead of high and the fontanelle depressed instead of bulging. After hydration or correction of the circulatory collapse, the increase in tension of the fontanelle will become apparent.

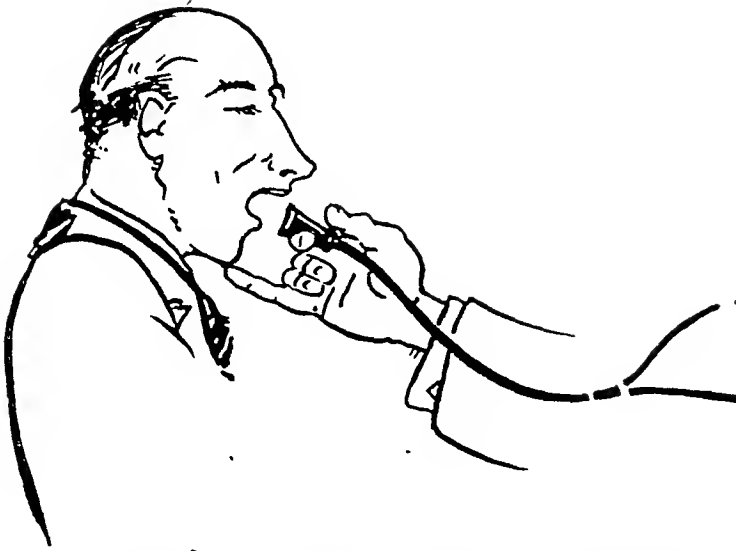
Examination of the Chest. The experienced physician knows that minimal tuberculosis is not detectable by the stethoscope and that for early diagnosis he must depend upon the timely chest film. He also knows that in examining the chest he must listen carefully for râles during the inspiration following a forced expiration and repeated cough. This procedure long known to chest specialists and taught in every school in the land is too frequently neglected in practice. The limitations of each method of examination must be learned. To master physical diagnosis of the chest, it is only necessary to have good eyes, good ears, one stethoscope,* a fluoroscope, a good roentgenographic unit, a ration of intelligence, a measure of determination and a mess of patients. Thereafter stethoscope in hand one moves repeatedly back and forth, back and forth between the patient and the film until the film can be faced without fear of surprising and therefore unpleasant revelations. *The roentgen-ray should be used not merely for diagnosis but as a teacher of physical diagnosis.*

Wheezing due to bronchial asthma is of long standing and is generally distributed. A localized wheeze of recent development is strongly suggestive of bronchial obstruction. This type of wheeze may also be heard with the bell of the stethoscope held about three inches in front of the open mouth of the patient (figure 4). The most common causes are bronchial tuberculosis, bronchial adenoma, endobronchial carcinoma, foreign body in the bronchus. Chevalier Jackson's dictum is worth remembering: "All is not asthma that wheezes."

In recent years one of the great advances in the diagnosis of diseases of the chest has been increasing recognition of collapse of part of a lung and its causes. For the final solution of these pulmonary problems, fluoroscopy, roentgenography, bronchoscopy and bronchography are indispensable. However, in routine physical examinations certain observations may be made quite easily to determine whether all parts of the lungs are well ventilated.

Does the chest expand equally on the two sides?

* Kerr's symballophone is a very useful instrument for the analysis of murmurs.



DON'T MISS THAT WHEEZE !

FIG. 4. Jackson's dictum is worth remembering: "All is not asthma that wheezes."

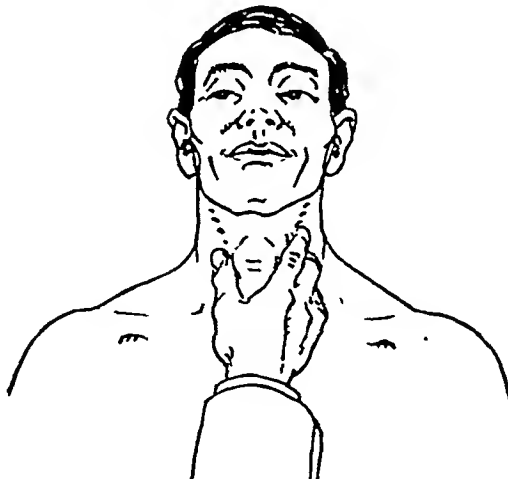
Is the trachea in the mid-line?

Where is the point of maximum apical impulse?

Do the two halves of the diaphragm move equally and what are their levels?

That movement of one side of the chest may be restricted in pneumonia, pleurisy with or without effusion, simple or complicated pneumothorax, old pulmonary tuberculosis is well known. To these should be added bronchial obstruction and the subsequent atelectasis of part or all of one lung.

The position of the trachea can be determined best by Gerald Webb's technic (figure 5). The examiner places the thumb of his right hand on the



GERALD WEBB'S TEST FOR DEVIATION OF TRACHEA

FIG. 5. In this test, the palpating "finger" is the thumb.

right side of the patient's neck between the larynx and the sterno-cleido-mastoid muscle and by gentle pressure on the thyroid cartilage determines its position and mobility much as in the vaginal examination the position and mobility of the cervix are determined. Then, the examiner swaps hands and places the thumb of his left hand in a corresponding place on the left side of the patient's neck between the larynx and the other sterno-cleido-mastoid muscle and again by gentle pressure toward the mid-line determines the position and mobility of the larynx and so the position of the trachea. The Holmes-Sellors test with a finger in the suprasternal notch is similar.

The significance of a Horner syndrome and unilateral or bilateral clubbing of the fingers will not be over-looked.

Is it part of the physical examination to look in the patient's sputum cup to see what sort of stuff is being raised? I think so! Most important information can be secured from simple naked-eye inspection of sputum and, it should be added too, by smelling it! (figure 6). The odor, appearance and



SPUTUM:

WHAT DOES IT LOOK LIKE?

IS IT FOUL SMELLING?

FIG. 6. The odor, appearance and the quantity of the sputum and their variations carry diagnostic and prognostic implications.

the quantity of the sputum and their variations carry diagnostic and prognostic implications. I have often said that I could tell with a fair degree of accuracy how the patients in a tuberculosis sanatorium were getting along by simple day after day inspection of their sputum cups.

The physician must not only have an inquiring mind, he must *cultivate* an inquiring mind. He must constantly ask himself why the patient has a rash, why he has a sore throat, why he has fever or what-not? Why does the patient have a "water-hammer pulse"? Does he have aortic regurgitation, patent ductus arteriosus, or coarctation of the aorta? To stimulate the student to exercise the inquisitive part of his brain I have built a lesson

around the phrase I just used—"the water-hammer pulse." A diagnosis of aortic regurgitation having been made, my inquiring mind subjects the inquiring mind of the student to the following inquisition:

"Why do you think this patient has aortic regurgitation?"

Answer: "Well, in the first place, he has a water-hammer pulse."

"Yes! He has a water-hammer pulse! By the way, what is a 'water-hammer'?"

Silence

There follows instruction to look up the meaning of the term "water-hammer," instruction how to make a "water-hammer" and finally orders to demonstrate the newly made water-hammer to the class at the next meeting. One is easily made with a test-tube, a little water and a bunsen-burner.

All this to the end that the student will be impressed with the thought that he must learn and practice the habit of inquiry.

The experienced physician will not miss a pulsus alternans with his finger on the radial artery but he will know how to check this observation with the sphygmomanometer. He will be familiar with normal and abnormal venous pulsations in the neck and will not confuse them with carotid arterial pulsations. He will not miss a pulsating liver and will know its significance. He will not miss a thrill because he failed to palpate for it with the patient sitting up, leaning forward with the breath held at the end of an expiration. He will not fail to listen to the heart with the patient lying down, sitting up, before and after exercise, and leaning forward with the breath held at the end of expiration.

Examination of the Abdomen. In examining the abdomen, he will not fail to have the patient point to the location of his pain. The experienced physician will look for liver enlargement in the mid-line as well as below the right costal margin. He will use Middleton's manoeuvre and will place the left hand and forearm of the patient under the left lower ribs as he palpates for an enlarged spleen.

He will not fail to make a careful neurological examination (figure 7) or to appraise the circulation in the legs, especially in the elderly patient. He knows that by simply moving the ulnar border of his hand gently over the surface of an extremity up and down foot to hip and back that he can with great accuracy define the limits of good circulation. Thomas Lewis' optimal thermo-tactile surface, the dorsal surface of the first phalanges, is generally most useful to detect surface temperature changes but is not as helpful for the specific purpose mentioned.

Our experienced physician will not miss a coarctation of the aorta because he did not compare the blood pressures in the lower extremities with those in the upper! He knows all about phlebothrombosis and thrombophlebitis and pulmonary embolism. He will measure repeatedly before and after operation the smallest circumference in the legs at the ankles and the largest at the

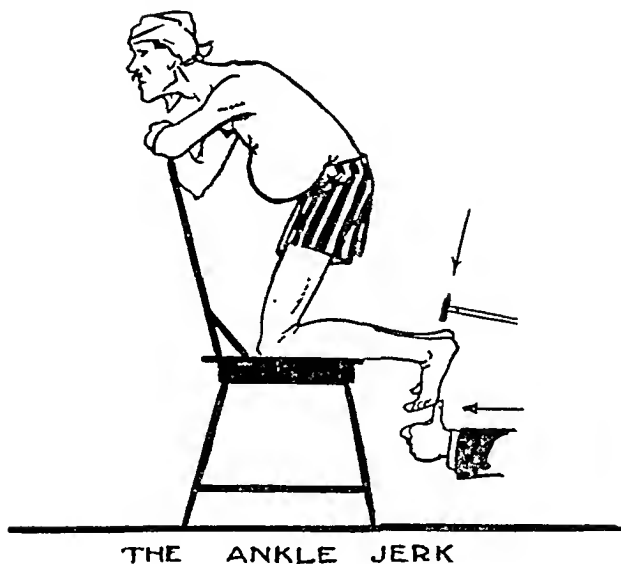
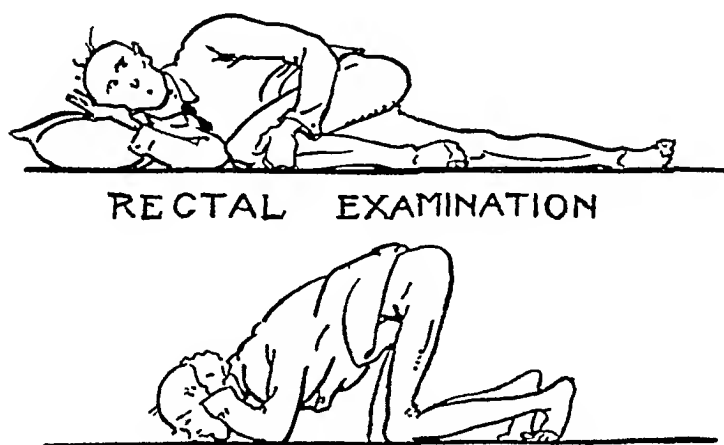


FIG. 7. A useful position for testing the ankle jerks.

calves, and will compare one leg with the other. He will watch for increased firmness or elasticity on compression of the calf, a tendency to resist dorsiflexion of the foot and tender points on the plantar surfaces of the feet. He knows that a thrombosed area in a superficial vein on the back of the calf is, in Homans' words, "a useful proof of deep thrombosis."

The Rectal Examination. Digital examination of the rectum is too often neglected. Hamilton Bailey phrases it unforgettably thus: "If you don't put your finger in it, you will put your foot in it" (figure 8).



" IF YOU DON'T PUT YOUR FINGER IN IT
YOU WILL PUT YOUR FOOT IN IT "
Bailey

FIG. 8. The digital examination of the rectum is too often omitted.

In children the abdominal examination may be unsatisfactory because the child is fearful it will be hurt. A careful digital examination of the rectum may reveal an acutely tender area on the right side and so establish a diagnosis of acute appendicitis. George Packard, Professor of Surgery at the University of Colorado, tells me that the anal sphincter in a child with generalized peritonitis from a ruptured appendix or in a child with appendiceal abscess has lost its tone and is lax. He considers this a very useful diagnostic sign. The rounded head of intussusception may be felt by digital examination of the rectum and the palpating finger will show the characteristic "currant jelly" smear of blood and mucus.

Approximately 12 per cent of all malignant tumors originate in the anus, rectum or sigmoid. In this region are located 80 per cent of all intestinal cancers, of which 85 per cent are within reach of the finger and diagnosis.

In doing the rectal examination, look for anal fissures, hemorrhoids, polyps, prostatic carcinoma, rectal carcinoma, fecal impaction, a rectal shelf of metastatic cancer. Remember that a fistula-in-ano may be tuberculous and that anesthesia of the anal canal with loss of tone of the internal sphincter and incontinence are characteristics of tabes and taboparesis. It is now quite convenient to remember that testicular insensitivity is a reliable sign of posterior column damage in tabes or taboparesis and you therefore seize the opportunity and the organ to test for it (figure 9). Joseph Earle Moore,

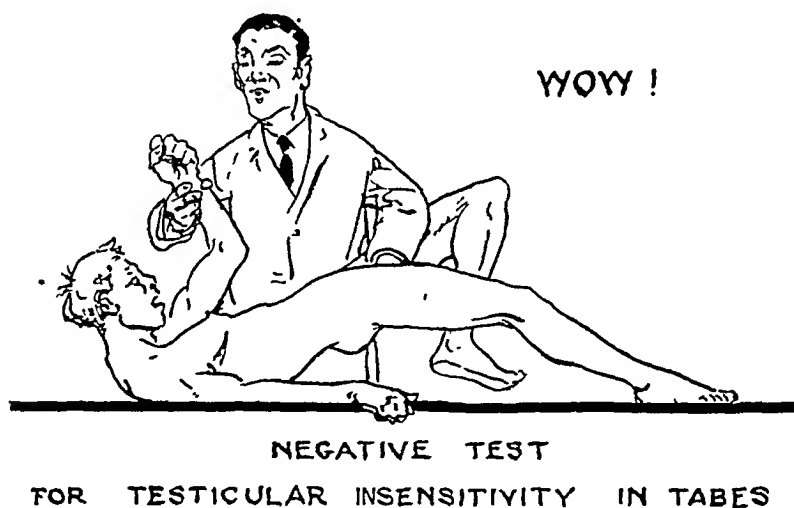


FIG. 9. Testicular insensitivity is a reliable sign of posterior column damage in tabes or taboparesis.

in a personal communication, says insensitivity of the testis "does not occur in any condition except those neurologic disorders in which deep pain sensation is lost. In many tabetics one can squeeze the testis almost to the point of rupture without producing any disagreeable sensations at all." Don't forget that a bimanual examination is useful in the male to discover a cancer

of the sigmoid. Look for tenderness in the pouch of Douglas in suspected ectopic pregnancy and tenderness in the right side of the pelvis in acute appendicitis.

So much by way of specific suggestions as to the physical examination! I would be very remiss if I did not now take you all the way back to the very beginning to emphasize one thing which, doubtless, is as well known to you as all the rest. John lies dead upon his bed. The difference between dead John and dead Richard is perhaps of interest only to the pathologist, but all those things which made the living John different from the living Richard are matters of the greatest concern to all physicians. Time was when these differences were important only to John and Richard and their friends, but of little significance to their family physicians. But, medicine has not stood still. All those things that made the living John different, his strengths and his weaknesses, his hopes and his fears, his joys and his disappointments, his yearnings, all his emotional as well as his organic reactions to his environment, all these things must be weighed by John's physician today, if he would help John! Mind and body have merged into one, the man John, friend, patient! I conclude, therefore, with this statement: The examination begins with the first greeting of the patient by his physician and does not wait the removal of the shirt.

SUMMARY

1. The five essentials to a good physical examination are: (1) a good light; (2) a favorable position of the patient; (3) a quiet environment; (4) a coöperative patient; (5) an experienced physician.

2. The importance of being sure that you have had an adequate "look," a satisfactory "feel" and an undisturbed "listen" is just as fundamental to good physical diagnosis in the adult as in the child.

3. The roentgen-ray should be used not merely for diagnosis but as a teacher of physical diagnosis.

4. Jackson's dictum is worth remembering: "All is not asthma that wheezes."

5. The odor, the appearance, the quantity of the sputum and their variations carry both diagnostic and prognostic implications.

6. The digital examination of the rectum is too often neglected. "If you don't put your finger in it, you will put your foot in it." (Hamilton Bailey.)

7. Finally, the examination begins with the first greeting of the patient by the doctor and does not wait the removal of the shirt.

URINE VOLUME AND TOTAL RENAL SODIUM EXCRETION DURING WATER DIURESIS *

By ANDREW J. CRUTCHFIELD, JR., and J. EDWIN WOOD, JR.,
Charlottesville, Virginia

THE value of drastically reducing sodium intake in treating the edema of congestive heart failure is generally accepted. Concerning the optimal water intake during such sodium restriction recommendations have ranged from the older view that fluids should be drastically restricted¹ to the opposite extreme, that fluids should be forced even to five or ten liters daily.² While many clinicians^{3, 4, 5, 6, 7, 8} favor a middle course and allow moderate or even ad libitum fluid intake, it would seem desirable to know how fluid intake might be adjusted to assure in the average patient the greatest possible excretion of sodium per day. On this important point no extensive studies have been made so far though the relation between chloride excretion and water diuresis has received some attention.²⁰

The important questions are (1) does water diuresis uniformly increase total sodium excretion above that observed with moderate urine flow? (2) does water diuresis enhance the sodium excretion produced by the common diuretic drugs? The studies here reported indicate that water diuresis per se increased sodium excretion if urine formation was previously low. If prior urine formation exceeded two to three liters per day water diuresis actually decreased the total excretion of sodium. It appears therefore that a maximal sodium excretion can be obtained in most cases with a moderate urinary volume viz, two to three liters per day. The effects of concomitant water diuresis on the action of diuretics are also considered.

Method. Water diuresis was produced by oral administration of 1,000 c.c. of tap water within 15 minutes. The subject was allowed no food or water after midnight the night before the test. The bladder was emptied at 7:30 a.m. and this specimen discarded. The 7:30 to 8:30 specimen was used as a control. Between 8:30 and 8:45, 1,000 c.c. of tap water were administered orally. Hourly urines were then collected until 1:30 p.m. During the test, the subject reclined quietly in bed except for transient assumption of the erect posture as needed to facilitate voiding.

One to three days later the test was repeated and in addition one of the following diuretic substances was added. (1) Theophylline 0.3 gram at 8:30 a.m. orally. (2) Theobromine calcium salicylate 3.0 grams at 8:30 a.m. orally. (3) Theophylline with ethylene diamine, 0.5 gram intravenously at 8:30 a.m. (4) Urea, 30 grams at 8:30 a.m. orally. (5) Glu-

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From the Department of Internal Medicine, School of Medicine, University of Virginia, Charlottesville, Virginia.

case, 75 c.c. of 50 per cent solution intravenously at 8:30 a.m. and (6) Mercurophylline injection, 2 c.c. intramuscularly at 7:30 a.m. Each substance was tested on a minimum of four patients.

The subjects were about equally divided as to sex and race (white and negro). All adult age groups were included but no patient was above 75 years of age. Urine volume was measured in cubic centimeters. Sodium determination was done with a flame photometer, direct method. The major observation on sodium excretion during water diuresis has been repeatedly checked by a gravimetric determination of sodium²¹ and the results of photometric studies confirmed. Approximately 100 observations on water diuresis and sodium excretion have been made on 50 patients.

TABLE I

Urine Volume and Total Renal Sodium Excretion during Water Diuresis in a Patient: (1) with Moderately Severe Congestive Failure; (2) at the Height of Diuresis under Rest and Digitalis and (3) Following Recovery from Failure

		1		2		3	
		Urine Volume c.c.	Total Sodium Mg.	Urine Volume c.c.	Total Sodium Mg.	Urine Volume c.c.	Total Sodium Mg.
Hours	5	150	46.7	280	233.4	—	—
	4	390	24.8	300	196.0	250	148.5
	3	200	14.6	350	89.9	525	110.2
	2	260	143.9	630	169.5	310	89.9
	1	100	180.9	290	388.0	260	162.2
Total		1100	410.9	1850	1076.8	1345	510.8

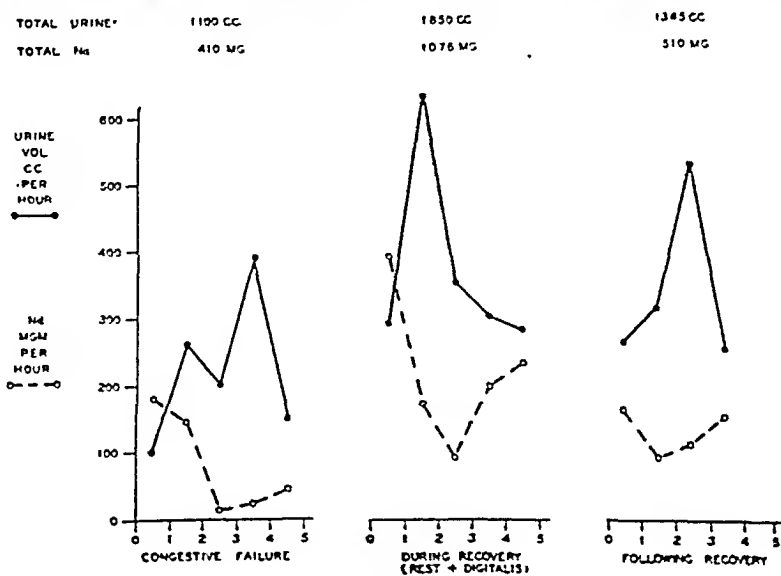


CHART 1.

Water Diuresis and Renal Sodium Excretion. From these experiments, a definite pattern of urine volume and total hourly renal sodium excretion has been recorded over a period of six hours during water diuresis. This pattern is essentially the same in outline for both normal and congestive heart failure patients although a quantitative difference does exist, that is, the urine volume and the total renal sodium excretion during water diuresis varied from high to fairly low values in patients with congestive failure, depending

TABLE II

Patient	Diagnosis	Urine Volume Control Hour	Mg. Na Control Hour	Urine Volume Peak Diuresis Hour	Mg. Na Peak Diuresis Hour
Group I					
1	Normal	29	48.7	470	40.4
2	Congestive failure	30	49.8	392	25.0
3	Normal	42	74.3	350	60.2
4	Conjunctivitis	58	187.4	460	135.7
5	Coronary insufficiency	72	191.2	310	88.3
6	Neurosis	74	319.3	626	257.8
7	Secondary Lues	82	187.0	512	147.4
8	Neurosis	90	200.0	410	45.0
9	Muscular dystrophy	112	299.6	669	235.4
10	Normal	113	210.1	434	163.6
11	Normal	126	241.0	158	143.7
12	Congestive failure	135	387.0	438	158.5
13	Normal	136	408	750	186.7
14	Neurosis	220	266	550	212.8
15	Normal	222	108.1	534	80.1
16	Neurosis	252	401.9	786	249.5
17	Neurosis	265	268.9	444	176.2
Group II					
1	Neurosis	10	30.2	275	277.1
2	Congestive failure	11	3.2	102	38.4
3	Normal	14	48	525	156.9
4	Normal	20	56.5	234	119.3
5	Neurosis	27	23.3	478	97.9
6	Normal	29	105.2	710	221.5
7	Neurosis	29	24.9	535	107.5
8	Congestive failure	30	32.8	157	94.9
9	Neurosis	30	110.5	450	154.8
10	Neurosis	31	151.9	785	257.4
11	Neurosis	33	117.1	650	138.4
12	Normal	34	57.1	682	113.2
13	Neurosis	35	166.4	684	305.3
14	Normal	36	126.0	634	181.3
15	Neurosis	38	69.6	670	137.3
16	Normal	38	79.0	494	172.4
17	Neurosis	42	174.9	434	216.5
18	Neurosis	42	104.7	473	160.8
19	Neurosis	49	56.2	838	180.1
20	Hypertension	51	129.5	412	197.7
21	Neurosis	57	178.2	605	248.0
22	Normal	74	109.5	470	131.6
23	Neurosis	99	21.7	518	126.3
24	Congestive failure	113	43.5	468	46.8

on such factors as the amount of edema,⁹ the relative state of cardiac competency at the time of the test, the amount of sodium in the diet, and the concentration of sodium in the plasma.^{9, 10, 11, 12, 13}

The effect of water diuresis on renal sodium excretion in a patient with hypertensive heart disease and moderately severe congestive heart failure is illustrated in table 1 and chart 1. Water diuresis was observed during: (1) Moderately severe failure (weight 165 pounds and venous pressure 200 mm. of water); (2) At the height of diuresis under rest and digitalis (weight 157 pounds and venous pressure 130 mm. of water); (3) When the patient was edema free and ready for discharge (weight 154 pounds and venous pressure 90 mm. of water). It is apparent that in each instance of water diuresis depression of total renal sodium excretion occurred just as in the normal subjects shown in Group I of table 2. Therefore, many of our experiments have been done on normal people for obvious reasons.

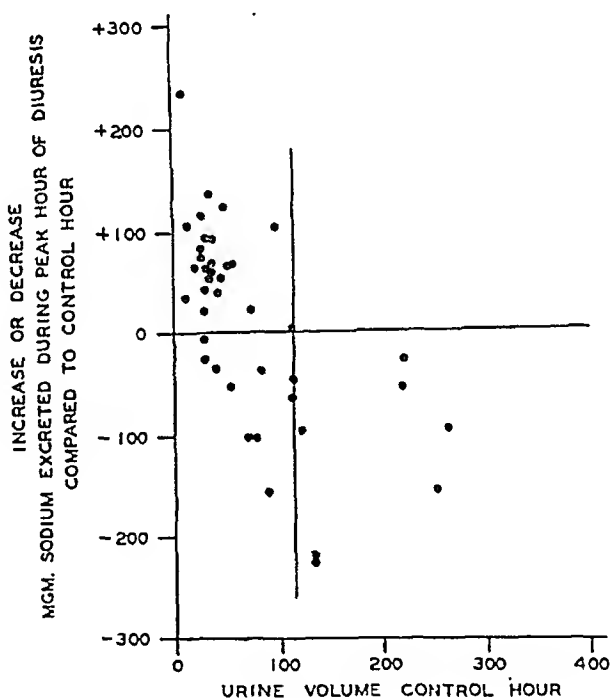


CHART 2.

A comparison is made in table 2 and chart 2 between the total renal sodium excretion during the control hour and during the hour of greatest urine volume. Of the 41 patients, 17 excreted more sodium during the control hour than during the hour of greatest diuresis. The other 24 patients excreted more sodium during the hour of greatest diuresis than during the control hour. The 17 patients will be referred to as Group I and the 24 patients as Group II. The striking difference in the two groups is the urine volume during the control hour with an average figure of 121 c.c. for Group I and 40.8 c.c. for Group II.

Therefore, in Group II urinary flow was below a level theoretically necessary for the adequate excretion of solids¹⁴ while in Group I urinary flow was up to or above adequate flow. Certainly half or more of Group II temporarily did not have enough urinary water during the control hour to excrete sodium and other solids ready for excretion. It seems likely therefore, that the increased sodium excretion at the height of diuresis in this group simply represents the elimination of sodium retained during inadequate urinary flow. Obviously the nature of the experiment does not permit finely adjusted controls and a certain amount of overlap does occur in the two groups. However, it would seem that there is a certain range of urinary volume necessary for the maximal excretion of sodium and above or below this level renal sodium excretion falls off. If adequate urinary flow had been present during the control hour then Group II patients would probably have excreted sodium during water diuresis as did the Group I patients. This problem may be approached in a slightly different fashion.

Total renal sodium excretion in 41 patients for the two hours of greatest urine volume and the two hours of smallest urine volume is shown in table 3.

TABLE III

Average urine volume and total renal sodium excretion during water diuresis in 41 patients for the two hours of smallest urine volume and the two hours of greatest urine volume

Smallest
257.4 c.c.
336.0 mg. Na

Greatest
799.4 c.c.
330.8 mg. Na

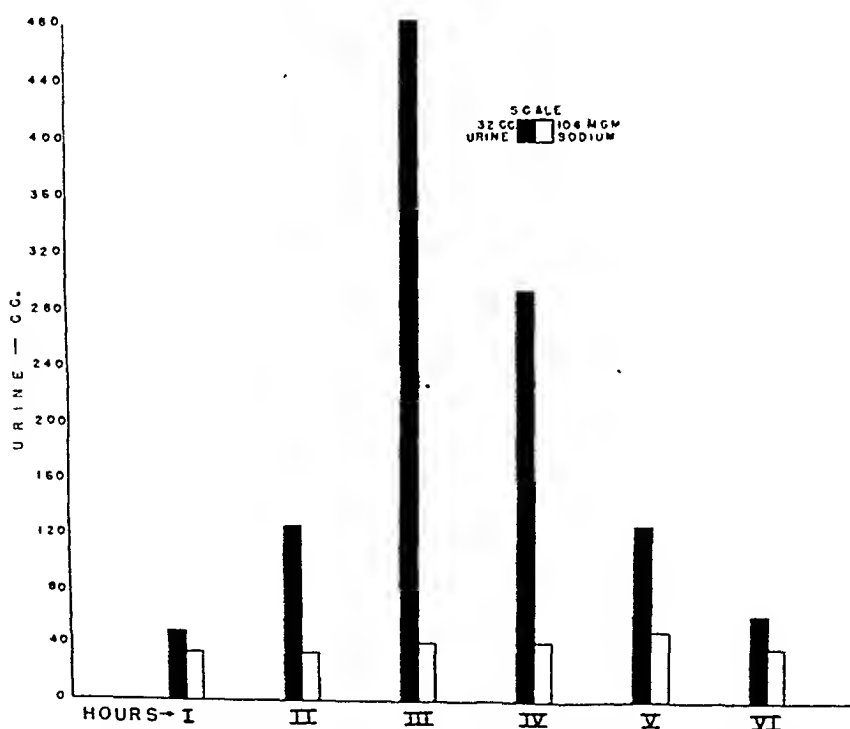


CHART 3. Water diuresis. Urine volume and total renal sodium excretion. Average finding in 32 patients.

In spite of the marked difference in urine volume (799.4 c.c. against 257.4 c.c.) the total renal sodium excretion is actually slightly less during the greatest urine volume period (330.8 mg. against 336.0 mg.). A composite presentation of the average urine volume and total renal sodium excretion for 32 patients over the six hour experimental period is shown in chart 3. As stated above, several of these patients had inadequate urine volume in the control hour, but in spite of this, the group figures show no significant increase in total sodium excretion at the peak of water diuresis. The hour of highest total renal sodium excretion follows the hour of greatest water

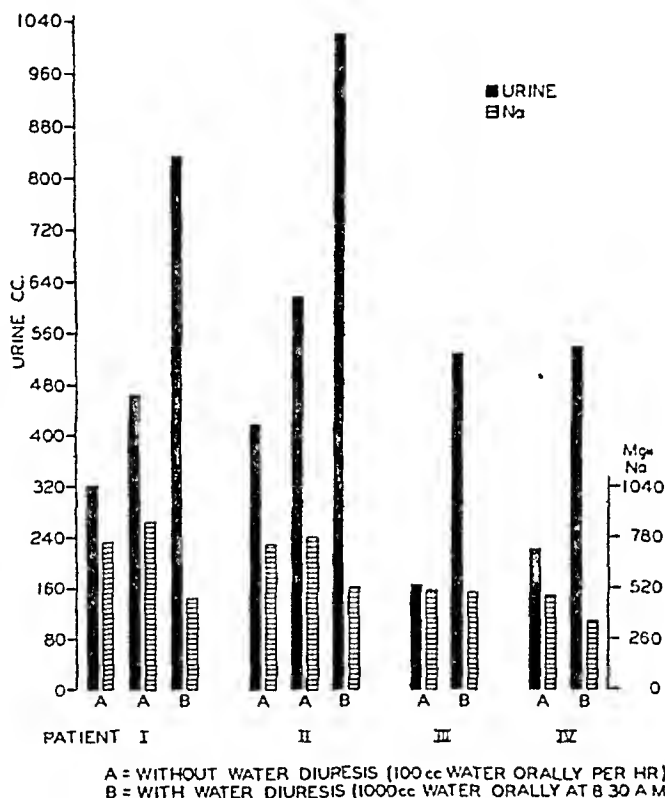


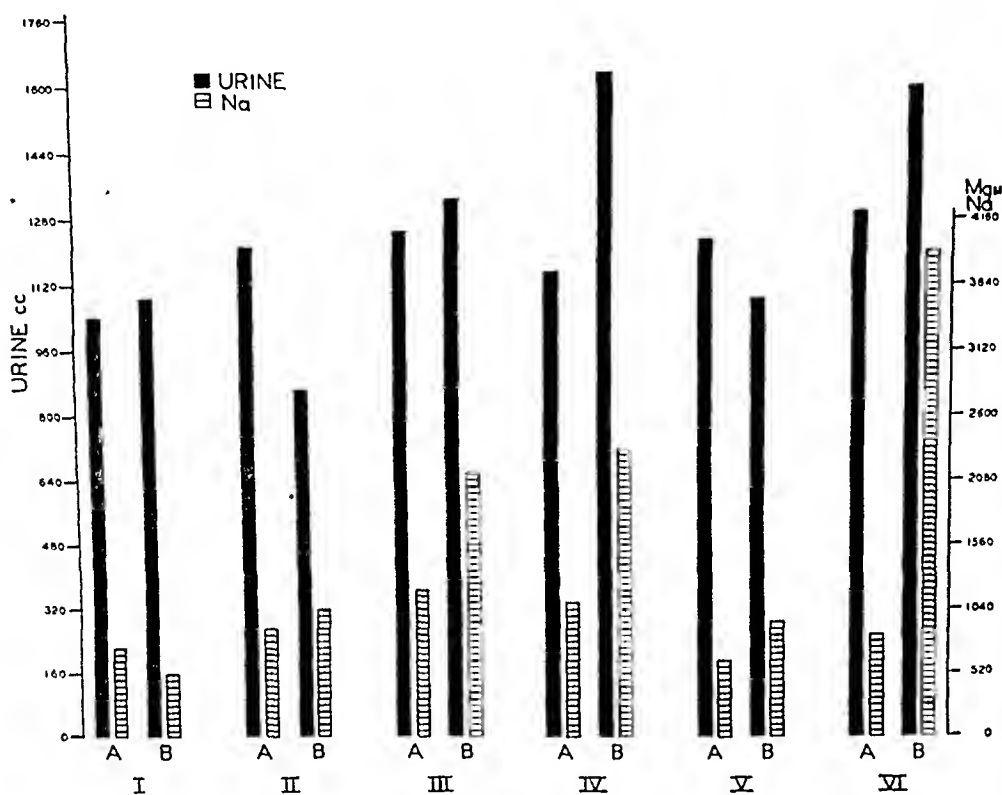
CHART 4. Urine volume and total renal sodium excretion.

diuresis. This may be due to the excretion of the sodium retained during the hours of marked diuresis.

Conceivably, such a reduction in sodium excretion during water induced diuresis could be caused by the post-prandial alkaline tide.¹⁶ However, this factor of food ingestion was reduced as far as possible by doing all tests in the fasting state. Indeed, the occurrence of water diuresis was probably proof that most of the sodium from the upper bowel returned to the extracellular spaces during absorption of the water. It could be argued further that the high sodium excretion during the early hours of this test was secondary to the morning alkaline tide, a condition thought to be associated with the primary carbon dioxide deficit on awakening and for several hours thereafter.¹⁷ Observations were accordingly made on urine volume and

total renal sodium excretion over the same six hour period on consecutive days with and without water diuresis. Chart 4 indicates that total renal sodium excretion under these conditions is again reduced by water diuresis.

It would appear then, that in a patient who already has adequate urine volume, the exhibition of water diuresis does not increase total renal sodium excretion but to the contrary, depresses it. Most of these patients were



EACH PAIR COLUMNS AB INDICATES AVERAGE FINDINGS OF FOUR TESTS ON FOUR PATIENTS

(A) 1000 cc. WATER ORALLY

(B) 1000 cc WATER ORALLY PLUS CERTAIN DIURETICS

I B - GLUCOSE 75 cc. 50% I.V.

II B - UREA 30 GRAMS

III B - THEOPHYLLINE ETHYLENE DIAMINE 0.5 GM. I.V.

IV B - THEOPHYLLINE 0.3 GM.

V B - THEOBROMINE CALCIUM SALICYLATE 3.0 GMS.

VI B - MERCUROPHYLLIN INJECTION 2 cc I.M.

CHART 5. Urine volume and total renal sodium excretion.

eating a regular diet¹⁵ and therefore, all were excreting approximately 40 to 50 grams of solids in the urine daily.

In the light of the observations recorded the question arises as to optimal water intake for the congestive heart failure patient. Data from patients 3 and 4 in chart 4 suggest that water diuresis depression of renal sodium excretion seems to begin when the urinary flow reaches an equivalent of about two liters in 24 hours. Further data bearing on this point appear in the Group I patients of table 2. Here at a calculated 24 hour urinary output of

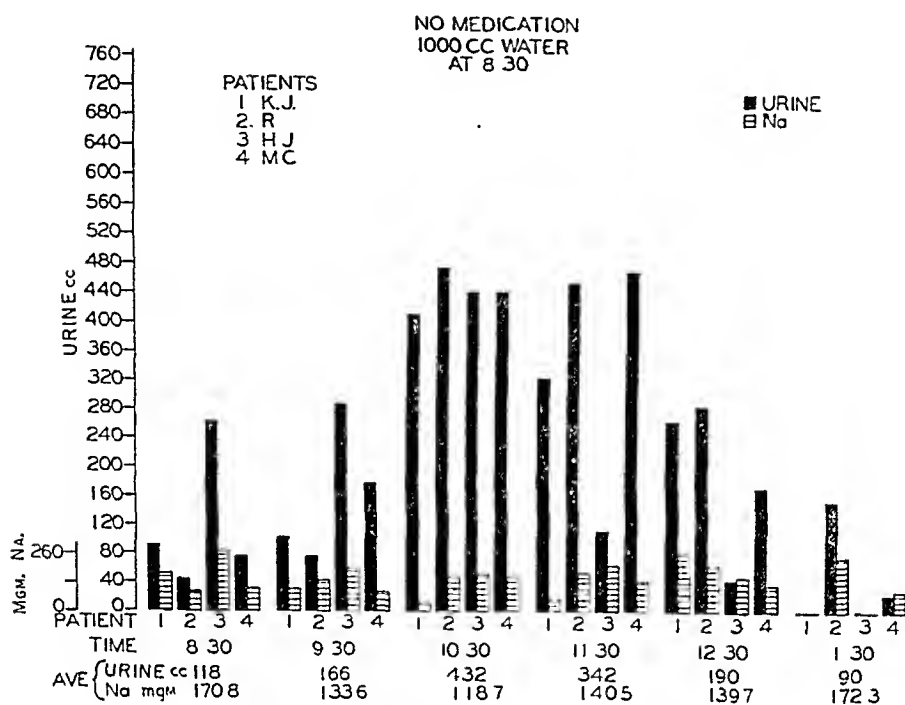


CHART 6 A.

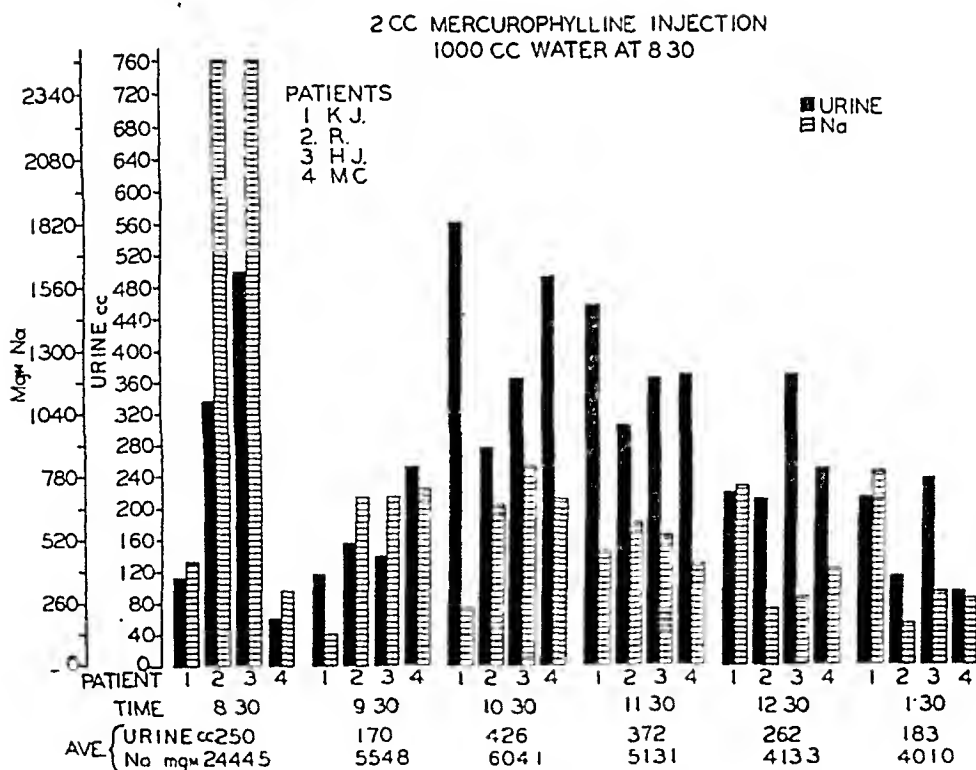


CHART 6 B.

approximately 2904 c.c. total renal sodium excretion was regularly diminished by a still further increase in urine volume. Apparently then, water as a diuretic loses its potentialities as a therapeutic aid in sodium excretion when urine volume has reached a level between two and three liters per 24 hours following increased water intake.

Water Diuresis Plus Certain Diuretics and Renal Sodium Excretion. If this pattern of urine volume and total renal sodium excretion seems reasonably constant for water diuresis then modification of sodium excretion theoretically should follow the administration of diuretic substances at an appropriate time during the experiment. This effect has been observed for a number of common diuretics.

Xanthines: Chart 5 reveals that intravenous theophylline with ethylene diamine is a potent diuretic even when combined with water diuresis. The striking effect, however, was not the relatively small increase in urine volume but rather the great increase in total renal sodium excretion. Theophylline produced similar effects. Theobromine calcium salicylate produced no appreciable increase in sodium excretion.

Mercuraphylline Injection: Charts 5, 6 A and 6 B indicate that like intravenously administered theophylline with ethylene diamine, this substance maintained its potency as a diuretic when combined with water diuresis. There was a similar disproportionate increase in urine volume and total renal sodium excretion favoring the latter. The great increase in total renal sodium excretion during the control hour in patients 2 and 3 shown in chart 6 B was due to improper timing of administration of the mercuraphylline injection.

Urea and Glucose: As might be expected these osmotic substances tended to lose their efficiency as diuretic agents when combined with a large water intake, as shown in chart 6. In all five of the patients studied, urea seemed to inhibit water diuresis to a slight degree, and correspondingly depressed total renal sodium excretion in three of the five patients. The other two patients showed slight increase in total renal sodium excretion. Glucose produced little effect. In two of the four patients, both water diuresis and total renal sodium excretion were diminished. In the other two, there was slight increase in water diuresis and total renal sodium excretion. The failure of glucose compared with urea may be related to its more rapid removal from the body fluids by oxidation and renal excretion.

DISCUSSION

Water diuresis seems to be based on inhibition of the posterior pituitary gland following relatively rapid dilution of the blood subsequent to water ingestion. It has been shown that water diuresis is associated with decreased total renal excretion of chloride.²⁰ Our experiments agree with this latter observation as regards sodium in those subjects who had adequate urine volume during the control hour preceding the experiment. The group of

patients (Group II) with inadequate urinary water during the control hour of the experiment increased their total renal sodium excretion during water diuresis.

The explanation for the depression of total renal sodium excretion during water diuresis is not apparent. It does not seem to be directly related to reduced plasma sodium concentration for the greatest plasma dilution as measured by plasma electrolyte concentration precedes the peak of water diuresis by 15 to 30 min.¹⁸ The fact that the greatest depression of renal sodium excretion usually occurs at the peak of water diuresis suggests that the water diuresis and the sodium retention are both mediated through the inhibition of the posterior pituitary.²⁸ Further evidence to support this thesis is found in the observation that renal sodium excretion is increased by the administration of posterior pituitary substance to normal patients³⁰ and to animals with diabetes insipidus.¹⁹ Pituitrin in 20 unit doses was tried in several patients during the present study but no striking increase in total renal sodium excretion was observed.

The rôle of the adrenal cortex in this regard stimulates speculation. In view of the known sodium retention effect produced by administration of adrenal cortical extract, it seems possible that the adrenal cortex may be stimulated by the same factor (that is, reduced plasma electrolyte concentration) which inhibits the production of the antidiuretic principle by the posterior pituitary. This point could probably be clarified were it not true that water diuresis cannot be produced in patients with Addison's disease and other hyponatremic states.¹³ Regardless of how this depression of total renal sodium excretion is mediated, the kidney apparently conserves sodium, as a prematurely compensatory action, favoring water shift from the intracellular to the extracellular compartment. Such a safety measure insures maximum use of total body water in the face of prolonged diuresis. This particular mechanism has been shown to operate in dogs having experimentally produced diabetes insipidus.²⁰

The similarity between the effects of certain xanthine drugs and a mercurial (mercurophylline injection) suggests that these substances have a common mode of action on the kidney, namely, that each depresses tubular reabsorption of sodium more than tubular reabsorption of water.^{22, 23} The increase in glomerular filtration rate as an explanation of diuresis following xanthine drugs has been disproved.³¹

In all five patients studied, urea inhibited water diuresis slightly. This seems to be based on a mechanism similar to the well known sodium chloride inhibition of water diuresis.^{23, 32} The distribution of urea throughout all body water and its large molecule render it less active than sodium chloride as an inhibitor of water diuresis. In addition to the tendency of glucose and especially urea to inhibit water diuresis these substances are rendered impotent in reducing edema when administered with a large volume of water for they are excreted in the concomitant urinary water without change in the

edema. The effect of urea and glucose on total renal sodium excretion was slight and unpredictable.

Although it is not the purpose of this study to investigate the mechanism or mechanisms underlying the development and maintenance of congestive heart failure, it has been found that many patients with chronic congestive heart failure have a low serum sodium concentration. This is shown by the following values in m. eq. per 1000 c.c. of serum obtained from patients with congestive heart failure: 131.4, 139.1, 135.1, 132.3, 132.7, 138.3, 137.0, 130.1, 137.3, 137.0, 129.6, 138.7, 137.4, and 134.8. These determinations were made in duplicate by the gravimetric method of Butler and Tuthill²¹ and may be compared with serum sodium values from normal people in the following series, done at the same time by the same method: 143.5, 142.4, 147.1, 139.8, 141.1, 140.9, and 140.9. That additional factors than the serum sodium concentration influence the amount of sodium excreted during the water diuresis period is indicated by the normal or greater than normal total renal sodium excretion in some of the above patients while serum sodium concentration remained low. The explanation of this low serum sodium concentration in congestive heart failure patients is not apparent. Such factors as prolonged use of a low sodium diet without corresponding restriction of water intake plus use of diuretics which enhance sodium excretion contribute to it.^{22, 23, 24, 25} Regardless of the mechanism of its developments, the very presence of low serum sodium concentration tends to cast doubt on retention of sodium as a primary event in the development of congestive heart failure.²⁶ If such a sequence does occur, naturally one would expect to find serum sodium concentration normal or slightly above normal.²⁷ On the other hand, with restricted sodium intake the congestive heart failure patient excretes a large intake of water with reasonable facility and this suggests that retention of the sodium ion is of nearer primary importance than retention of water. This matter stands in need of further investigation.

CONCLUSION

1. It would appear from these data that, in a patient who already has adequate urine volume, the exhibition of water diuresis does not increase total renal sodium excretion. To the contrary, in such a patient, water diuresis usually decreases total renal sodium excretion.

2. It is further suggested that the optimal urine volume for the patient with congestive heart failure, when related to water diuresis alone, falls between two and three liters daily.

3. The efficiency of osmotic diuretics is markedly impaired in edema reduction when combined with water diuresis.

4. Xanthines and mercuraphylline injection disproportionately increase urinary volume and total renal sodium excretion favoring the latter. This suggests the primary renal action of these substances may be depression of tubular reabsorption of sodium.

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THE INCIDENCE OF HEART DISEASE IN 2,000 CONSECUTIVE AUTOPSIES *

By WILLIAM B. WARTMAN, M.D.,† *Chicago, Illinois*, and HERMAN K.
HELLERSTEIN, M.D.,‡ *Cleveland, Ohio*

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From the Institute of Pathology, Western Reserve University and University Hospitals of Cleveland.

† Present address: Department of Pathology, Northwestern University Medical School, Chicago, Ill.

‡ Present address: University Hospitals, Cleveland, Ohio.

Tumors
Valvulitis, Non-rheumatic
Acute Endocarditis
Chronic Non-rheumatic Valvulitis
Air Emboli

THIS report is a statistical study of the incidence of heart disease in 2000 consecutive autopsies performed at the Institute of Pathology, Western Reserve University, from January 28, 1935, to April 4, 1940. These autopsies were on patients who died at Lakeside Hospital (422 beds), Babies and Childrens Hospital (150 beds) and Maternity Hospital (150 beds). All autopsies were performed under the supervision of an experienced pathologist and the final diagnoses were made by him. Anatomical diagnoses were used in making the tables and when it was desirable the diagnoses were checked with the gross descriptions and microscopic slides.

The term "heart disease" is used in an anatomical sense and includes all organic lesions of the pericardium and heart, but it does not necessarily mean clinically evident disease. The criteria set forth by the New York Heart Association⁶ are used for both clinical and anatomical diagnoses.

The cardiac lesions were divided into four main groups as follows: (1) Rheumatic heart disease; (2) hypertensive heart disease; (3) coronary artery disease; and (4) miscellaneous. Each of these groups has been subdivided as shown in the tables. Obviously some cases could be put into more than one group, but in order to avoid confusion each case has been listed only once, in the group which was judged to be the most important. For example, nine patients with serious rheumatic heart disease also had mild hypertension. Accordingly, they were classified as rheumatic heart disease.

The group with rheumatic heart disease included only cases with deforming lesions. Not included were cases of chronic non-deforming valvulitis which is now considered as probably due to rheumatic fever.⁴

The group with hypertensive heart disease consisted of patients who during life had persistent elevation of blood pressure and of patients who showed enlargement of the heart with either chronic pyelonephritis, arterial and arteriolar nephrosclerosis or glomerulonephritis. When only terminal blood pressure readings were available the cases were not included unless there was anatomical evidence of previous hypertension. The subgroup "without coronary artery disease" includes cases in which there was either no arteriosclerosis at all or only an occasional intimal plaque which did not obstruct the lumen.

The main group "coronary artery disease, without hypertension" has three subgroups. The first includes cases with slight to moderate arteriosclerosis, associated with myocardial fibrosis; the second, cases with marked stenosis or occlusion due either to arteriosclerosis, thrombosis, intramural hemorrhage or some other cause; the third, cases with endarteritis and periarteritis nodosa. Occlusion is used in the sense of complete obstruction of the lumen.

AGE, SEX AND COLOR

Table 1 gives the general incidence of the different anatomical lesions which were discovered at autopsy, and subsequent tables give details of observations in the various groups. Eighty per cent of the 2,000 cases were white, and 20 per cent negro. In each group 64 per cent were males and 36 per cent females. Thirty-six per cent of the patients were under 40 years of age, and 16 per cent of them were under five years. Most of the latter group were premature or newborn babies. The age curve of this series (chart 1) was almost identical with the curve of deaths from all causes in the United States Registration Area for 1940,¹² indicating that our data were representative of deaths in the country as a whole.

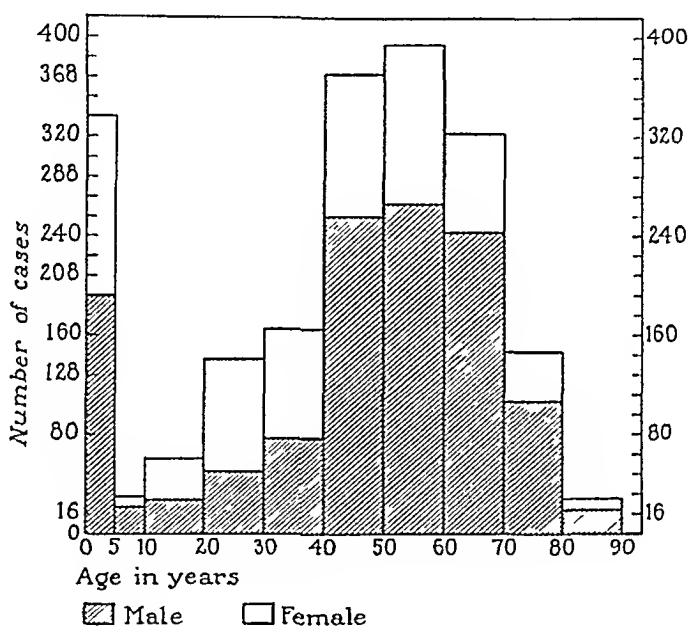


CHART 1. Age, sex distribution of 2,000 consecutive autopsies.

If congenital heart disease is excluded, 984 (49.2 per cent) of the patients had a cardiac lesion (table 1), although not all the lesions were sufficiently important to have contributed to death. Clinical heart failure was noted in 38.9 per cent of these 984 cases (table 2). On the other hand, 505 patients (25 per cent) had heart disease which had been diagnosed clinically, of whom 383 (76 per cent) died with some degree of clinical heart failure. Thus, 76 per cent of those who had clinically evident heart disease had some degree of failure at the time of death, while 19 per cent of the total autopsy group died directly of heart failure.

Comparison of Clinical and Anatomical Diagnoses in Patients Who Died in Heart Failure. Table 3 lists the cardiac lesions in 383 patients who died in failure, and a comparison is made with the clinical diagnoses. Clinical acumen was attested by the high correlation between antemortem and post-

TABLE I

Incidence of Cardiac Lesions in 2,000 Consecutive Autopsies
(Exclusive of Congenital Heart Disease)

	Number of Cases	Per Cent of Cases with Heart Disease	Per Cent of Total Autopsy Population
Rheumatic Heart Disease	120	12.2	6.0
Rheumatic heart disease alone	104	10.6	5.2
Rheumatic heart disease with endocarditis lenta	16	1.6	0.8
Hypertensive Heart Disease	271	27.5	13.6
Without coronary artery disease	77	7.8	3.8
With coronary artery and myocardial disease	194	19.7	9.7
Coronary Artery Disease (without hypertension)	272	27.6	13.6
Coronary arteriosclerosis with myocardial fibrosis	139	13.9	6.9
Stenotic sclerosis, with myocardial fibrosis and infarcts	122	12.4	6.1
Coronary arteritis	11	1.1	0.6
Miscellaneous	321	32.6	16.0
Syphilitic heart disease	20	2.0	1.0
Cor pulmonale	18	1.8	0.9
Pericarditis	52	5.3	2.6
Cardiac hypertrophy, unknown etiology	16	1.6	0.8
Fat infiltration	33	3.3	1.6
Fatty degeneration	30	3.0	1.5
Myocarditis	33	3.4	1.7
Atrophy of heart	19	1.9	1.0
Neoplasm of the heart	16	1.6	0.8
Valvulitis (non-rheumatic)	39	4.0	2.0
Others	45	4.7	2.2
Total	984	100.0%	49.2%

mortem diagnoses in those patients who died in heart failure. There was a tendency to make the diagnosis of arteriosclerotic heart disease in cases of rheumatic heart disease, to overlook myocardial infarcts in hypertensives as well as non-hypertensives, and to diagnose syphilitic heart disease too frequently in rheumatic aortic valvulitis. These results are similar to those of Scott and Garvin.⁸

HYPERTENSIVE HEART DISEASE

Table 4 gives the data for this group. All patients had clinical hypertension and at autopsy a heart which weighed 400 grams or more. Coincident dilatation was present in most cases. Cases of valvular disease with deformity, and nine cases in the group with rheumatic heart disease who also had slight hypertension, were not included.

Only 77 (29 per cent) cases with hypertension had simple uncomplicated enlargement of the heart, whereas 194 (71 per cent) of them had associated coronary artery disease. The incidence of coronary thrombi, myocardial

TABLE II

Incidence of Clinical Heart Failure in Organic Heart Disease Diagnosed at Autopsy

	Number of Autopsy Cases	Clinical Heart Failure	Per Cent Died in Failure
Rheumatic Heart Disease	120	90	75.0
Rheumatic heart disease alone	104	76	73.1
Rheumatic heart disease with endocarditis lenta	16	14	87.5
Hypertensive Heart Disease	271	145	53.5
Without coronary artery disease	77	52	67.6
With coronary arteriosclerosis, with thrombi and infarcts	194	93	47.9
Coronary Artery Disease (without hypertension)	261	100	38.3
Coronary arteriosclerosis, myocardial fibrosis (arteriosclerotic heart disease)	139	40	28.8
Coronary arteriosclerosis with occlusion and infarct	122	60	49.2
Miscellaneous	332	48	14.4
Syphilitic heart disease	20	13	65.0
Cor pulmonale	18	8	44.4
Pericarditis	52	7	13.4
Valvulitis (non-rheumatic)	39	3	7.7
Others	203	31	15.2
Total	984	383	38.9

TABLE III

Comparison of Clinical and Anatomical Diagnoses of 383 Patients Dying
in Clinical Heart Failure

	Per Cent Clinical Heart Diagnoses	Per Cent Autopsy Heart Diagnoses
Rheumatic Heart Disease	21.9	23.5
Rheumatic heart disease alone	16.7	19.1
with endocarditis lenta	4.7	3.7
with acute bacterial endocarditis	0.5	0.7
Hypertensive Heart Disease	35.5	37.9
Hypertensive heart disease alone	11.5	13.6
Hypertensive heart disease with coronary arteriosclerosis	12.5	8.6
Hypertensive heart disease with coronary occlusion and infarct	11.5	15.7
Coronary Artery Disease (without hypertension)	27.7	26.1
Coronary arteriosclerosis (arteriosclerotic heart disease)	12.8	10.4
Coronary arteriosclerosis with occlusion and infarct	14.9	15.7
Miscellaneous	14.9	12.5
Syphilitic heart disease	5.7	3.4
Cor pulmonale	2.1	2.1
Pericarditis, constrictive	2.6	1.8
Acute bacterial endocarditis	0.3	0.7
Embolism of right ventricle	0.3	1.0
Thyroid heart disease	0.7	0.0
Others	3.2	3.5

infarcts and fibrosis, which is shown in table 4, needs no comment. Thrombosis without infarction, and infarction without thrombosis will be discussed later. There were 11 cases of valvular disease without deformity and of undetermined etiology in the subgroup "coronary arteriosclerosis with myocardial fibrosis."

TABLE IV
Hypertensive Heart Disease

	Number of Cases
Simple hypertrophy and dilatation <i>without</i> coronary arteriosclerosis	77
With coronary arteriosclerosis	52
coronary arteriosclerosis with myocardial fibrosis	37
coronary arteriosclerosis with thrombi and infarcts	62
coronary arteriosclerosis with thrombi, <i>no</i> infarcts	3
coronary arteriosclerosis with stenosis and infarcts, <i>no</i> thrombi	29
coronary arteriosclerosis with stenosis and myocardial fibrosis	11
Total	271

Referring again to table 2, it is interesting to note that 47.9 per cent of the hypertensive patients who had coronary arteriosclerosis, thrombosis and infarcts, died in clinical heart failure. But as 49.2 per cent of non-hypertensive patients, who had similar coronary artery disease, also died in failure, hypertension evidently did not increase the chances of dying in heart failure in this series.

RHEUMATIC HEART DISEASE

The age, sex and color distribution of 120 cases of rheumatic heart disease are presented in table 5. Eighty-six of these cases had severe valvular deformities and the remainder only slight deformity. Forty-nine cases (41 per cent) of rheumatic carditis lived to be 45 years old or more. This does

TABLE V
Age, Sex, Color Distribution of 120 Cases of Rheumatic Heart Disease
(Includes 16 cases with endocarditis lenta, and 9 cases with hypertension)

Age	White		Colored		Total
	Male	Female	Male	Female	
Under 5 years	1	0	0	0	1
5-14	4	6	2	1	13
15-21	6	2	1	3	12
25-34	11	7	2	3	23
35-44	8	9	2	3	22
45-54	13	8	0	0	21
55-64	7	12	0	0	19
65-74	5	2	1	0	8
75-84	1	0	0	0	1
Total	56	46	8	10	120

not include cases now called healed non-deforming valvulitis.⁴ Thirty-four of the cases were active, of which nine were acute and without evidence of previous rheumatic carditis, and 25 had acute verrucous endocarditis superimposed on a chronic process. Involvement of the various valves is shown in table 6. The mitral valve was involved in every case, the aortic in 85,

TABLE VI
Valvular Involvement in 120 Cases of Rheumatic Heart Disease

	Number of Cases
Mitral and aortic	47
Mitral, aortic and tricuspid	26
Mitral alone	18
Mitral and tricuspid	14
Mitral, aortic, tricuspid and pulmonic	11
Mitral, tricuspid and pulmonic	2
Mitral, aortic and pulmonic	1
Mitral and pulmonic	1
Total	<hr/> 120

the tricuspid in 53, and the pulmonic in 15 cases. In 65 cases with severe valvular stenosis, the mitral valve was affected in 62 instances; 31 cases alone, 23 associated with aortic, five with tricuspid and aortic, and three with tricuspid involvement. The aortic valve was attacked in 31 cases; alone three times, with the mitral 23 times, with mitral and tricuspid five times. The tricuspid valve was involved in eight cases only. In no case was there pulmonary stenosis. The frequency of deforming involvement of the valves in rheumatic fever was in the order mitral, aortic, tricuspid and pulmonic. The incidence of coronary arteriosclerosis or thrombosis in this small series apparently did not indicate a trend for precocious occlusive disease in rheumatic fever. The incidence of coronary artery disease (table 7) in 30 per

TABLE VII
Incidence of Coronary Artery Disease in 120 Cases of Rheumatic Heart Disease

	Number of Cases
With coronary artery disease	36
Rheumatic heart disease with coronary arteriosclerosis	30
Rheumatic heart disease with coronary thrombi and infarcts	3
Rheumatic heart disease with coronary emboli, no infarct	1
Rheumatic heart disease with rheumatic coronary arteritis	2
Without coronary artery disease	<hr/> 84
Total	<hr/> 120

cent of cases with rheumatic heart disease was almost the same as the incidence of coronary artery disease in the total autopsy group, namely 25 per cent.

ENDOCARDITIS LENTA

Sixteen cases of endocarditis lenta were encountered among the 120 cases of rheumatic heart disease (13 per cent). They were equally divided as to

sex. Thirteen were white, three colored. Thirteen cases fell in the age group 15 to 34 years and the other three cases were between 35 and 54 years. The mitral valve was involved in 13 cases; four cases alone, six with the aortic and three with the aortic and tricuspid. The aortic valve was involved two times alone. The valves were markedly deformed in 11 cases, and slightly in five. There were three cases of myocardial infarcts probably of embolic origin, with no significant coronary artery disease.

CORONARY ARTERY DISEASE

Cases with coronary artery disease made up the largest group of the series. Counting the cases included in the hypertensive and rheumatic groups, the coronary arteries were significantly diseased in 502 (51 per cent) of the 984 cases with heart lesions or 25 per cent of the 2,000 autopsies.

TABLE VIII
Coronary Artery Disease (without Hypertension)

	Number of Cases
Coronary arteriosclerosis, uncomplicated	59
Coronary arteriosclerosis with myocardial fibrosis and cardiac hypertrophy	68
Coronary arteriosclerosis with myocardial fibrosis, <i>without</i> hypertrophy	11
Coronary arteriosclerosis, with thrombi, infarcts and hypertrophy	50
Coronary arteriosclerosis with thrombi and infarcts, <i>without</i> hypertrophy	4
Coronary arteriosclerosis with thrombi, <i>no</i> infarcts, with hypertrophy and dilatation	20
Coronary arteriosclerosis, with stenosis and infarcts, and hypertrophy, <i>no</i> thrombi	8
Coronary arteriosclerosis with stenosis, myocardial fibrosis, hypertrophy and dilatation	41
Coronary endarteritis obliterans with myocardial infarcts	4
Coronary periarteritis nodosa	3
Coronary arteritis, granulomatous, tuberculous, necrotizing	4
Total	272

Table 8 gives the pertinent data. The group includes (1) all cases with moderate or marked stenosis, and (2) all cases of occlusion whether due to arteriosclerosis, thrombosis, intramural hemorrhage or some other cause.

The heart was enlarged in 187 cases (69 per cent). The incidence was higher in cases with marked coronary artery disease. The sequence of events appeared to be coronary arteriosclerosis, stenosis of the lumen, ischemia of myocardium, dilatation of the heart, myocardial fibrosis, hypertrophy, thrombosis and infarction. There were only four cases with thrombi and infarcts which did not show hypertrophy. There were 14 cases of valvular and endocardial fibrosis without deformity and of undetermined etiology in the subgroup "coronary arteriosclerosis with myocardial fibrosis and cardiac hypertrophy and dilatation."

MYOCARDIAL INFARCTS AND CORONARY OCCLUSION

An analysis was made of the data with reference to the occurrence of myocardial infarcts and of occlusion of the coronary arteries. For the sake of clarity the subject will be discussed under the following headings: (1) Incidence of infarcts; (2) etiology of occlusions; (3) location of infarcts; (4) site of occlusion; (5) correlation of occlusions and infarcts; (6) associated lesions (complications) in the heart.

Incidence. The incidence of myocardial infarcts in the total autopsy group of 2,000 cases was 8.2 per cent. Table 9 shows the incidence of myo-

TABLE IX

Incidence of Myocardial Infarcts in Coexistent Heart Diseases

	Number of Cases
Rheumatic heart disease	3
with coronary thrombi and infarcts	3
Coronary artery disease (non-hypertensive)	66
Coronary thrombi and infarcts	54
Coronary arteriosclerosis with infarcts	8
Endarteritis obliterans with infarcts	4
Hypertensive heart disease	91
Coronary thrombi with infarcts	62
Coronary arteriosclerosis with infarcts	29
Endocarditis lenta	3
Embolic myocarditis with infarcts	3
(No coronary artery disease)	
Polycythemia with infarcts	1
Total	<hr/> 164

cardial infarcts in coexistent heart disease based on records of 160 cases which were considered adequate for critical analysis. Table 10 gives the age, sex and color incidence of cases with infarct. In order to evaluate these data it is necessary to know the incidence of males and females in the general autopsy population, as well as in the series under discussion. In the 2,000 consecutive autopsies there were 1280 males and 720 females, a ratio of 1.8 to 1. In the 160 cases in the series, 119 were males (8 colored) and 41 females (9 colored) which is a ratio of 2.9 to 1. There were 143 white and 17 colored patients which is a ratio of 8.4 to 1 in the series of 160, while the ratio in the autopsy population was 4 to 1. With this information the data in table 10 can be summarized as follows: single infarcts were more common in men than women (74 men to 20 women); multiple infarcts were proportionately more common in women than men (45 men to 21 women). Infarcts were relatively more common in colored than white women. Fewer infarcts were found in negroes than would be expected from the race incidence.

The relative incidence of hypertension in cases with single and multiple infarcts was the same. The frequent occurrence of hypertension in females with myocardial infarction is consistent with general experience (table 11). Many non-hypertensive women had associated diabetes mellitus and severe generalized arteriosclerosis. In the group of 160 cases, 235 infarcts of the

TABLE X
Age, Sex, Color Incidence in 160 Cases of Myocardial Infarct

Single Myocardial Infarct					
Age	White		Colored		Total
	Male	Female	Male	Female	
25-39	2	1	0	0	3
40-44	2	0	2	1	5
45-54	18	2	1	2	23
55-64	29	4	0	1	34
65-74	14	6	0	0	20
75-84	6	2	0	0	8
85	0	1	0	0	1
Total	71	16	3	4	94

Multiple Myocardial Infarcts					
Age	White		Colored		Total
	Male	Female	Male	Female	
25-39	0	0	0	0	0
40-44	1	0	1	1	3
45-54	9	2	3	1	15
55-64	17	6	1	2	26
65-74	8	5	0	1	14
75-84	4	3	0	0	7
85	1	0	0	0	1
Total	40	16	5	5	66

myocardium were accurately located by gross dissection. The distribution of infarcts is shown in table 12. Of patients with more than one infarct, 57 had two and nine had three infarcts.

Etiology of Occlusions. Factors which caused occlusion or obstruction of the coronary arteries and resulted in myocardial infarcts are shown in table 13. Most cases in the group "coronary thrombosis" also had moderate to severe arteriosclerosis. The incidence of intramural hemorrhage was about the same as previously reported by Wartman,¹⁰ accounting for 11 per cent of coronary artery obstruction in cases with infarcts.

TABLE XI
Incidence of Hypertension in 160 Cases of Myocardial Infarcts

	White		Colored		Total Cases
	Male	Female	Male	Female	
Hypertensive	54(34%)	24(15%)	7(4%)	8(6%)	93(58%)
Non-hypertensive	57(36%)	8(6%)	1(0.6%)	1(0.6%)	67(42%)
Total	111	32	8	9	160

TABLE XII
Location of 235 Myocardial Infarcts in 160 Patients

Location	Number of Infarcts	Per Cent of Infarcts	Number of Cases	Per Cent of Cases
Right atrium	15	6.4	15	9.4
Left atrium	2	0.9	2	1.3
Left ventricle	196	83.4	152	95.0
Anterior surface of left ventricle	120			
anterior surface, entire	4			
anterior apical	43			
anterior apical and anterior	45			
interventricular septum				
anterior apical and posterior	3			
papillary muscle				
anterior apical, lateral	9			
anterior basal, lateral	3			
anterior basal	4			
anterior ventricular septum alone	5			
Lateral surface of left ventricle	8			
Posterior surface of left ventricle	68			
posterior surface, entire	7			
posterior apical	8			
posterior basal	29			
posterior basal and posterior	9			
interventricular septum				
posterior basal and posterior	2			
papillary muscle				
posterior interventricular septum	2			
posterior lateral and posterior	11			
interventricular septum				
Right ventricle	22	9.3	22	13.8
Anterior surface				
anterior surface, entire	2			
anterior apical and anterior	9			
interventricular septum				
anterior basal	1			
Posterior surface				
posterior basal and posterior	9			
interventricular septum				
posterior lateral	1			
Total	235	100.0		

Table 14 lists the factors concerned in obstruction (not necessarily accompanied by infarct) of the coronary arteries in the total autopsy group. In 2,000 autopsies there were 247 cases of marked stenosis of one or both coronary arteries, an incidence of 12.4 per cent. In a previous report,¹¹ the incidence in 6,800 autopsies was 4.4 per cent. This difference is due to more thorough routine dissection of the coronary arteries in the present study.

Location of Myocardial Infarcts. The infarcts were located with reference to the anterior, lateral or posterior, and apical or basal portions of the various heart chambers (table 12) and not with reference to the muscle bundles, because information about muscle bundle localization was not included in the protocols. The left ventricle was the most frequent site of an infarct, being involved in 152 of 160 cases. In the eight cases in which the left ventricle was not involved, infarcts were present in the right atrium and right ventricle in four cases each.

TABLE XIII
Causative Factors in 164 Cases of Myocardial Infarcts

	Number of Cases	Per Cent of Cases
Coronary thrombosis	101	61.6
Coronary thrombosis and myocardial infarcts		
in group coronary artery disease	43	
in group hypertensive heart disease	55	
in group rheumatic heart disease	3	
Intramural hemorrhage	18	11.0
Intramural hemorrhage and myocardial infarcts	11	
Intramural hemorrhage, thrombosis and infarcts	7	
Coronary arteriosclerosis without thrombosis	41	25.0
Endarteritis obliterans	4	
Occlusive arteriosclerosis with infarcts	13	
Marked stenotic arteriosclerosis with infarcts	13	
Mild to moderate sclerosis with infarcts	11	
Polycythemia	1	2.4
Endocarditis lenta (mycotic infarct)	3	
Total	164	100.0

The anterior half of the interventricular septum was involved in 54 per cent of cases which had an infarct of the anterior portion of the left ventricle. When the infarct was posterior, 25 per cent showed involvement of the posterior half of the interventricular septum. In five cases the interventricular septum was involved alone. The lateral aspect of the left ventricle was seldom involved alone, for of 33 cases, 25 occurred in combination with infarcts of the anterior-apical or posterior-basal areas (76 per cent). In 21 cases infarcts were located in both anterior-apical and posterior-basal regions. In each case one infarct was fresh and the other old.

Infarcts were found in the right ventricle in 22 cases (13.8 per cent). These cases have been divided into three groups: (1) pure, four cases; (2)

TABLE XIV
Factors Concerned in Obstruction of the Coronary Arteries in 2,000 Consecutive Autopsies

Lesion	Number of Cases	Per Cent of Cases
Embolism	1	0.4
Inflammation	13	5.3
Rheumatic arteritis	2	
Periarteritis nodosa	7	
Endarteritis obliterans	4	
Syphilis (stenosis of coronary ostia)	2	0.8
Coronary thrombosis		
(alone or with intramural hemorrhage)	142	57.5
Coronary arteriosclerosis with stenosis *	89	36.0
With myocardial infarcts	37	
Without myocardial infarcts	52	
Total	247	100.0

* Stenosis means reduction in diameter of lumen to one-half or less.

overflow, or extension from the left ventricle, eight cases; and (3) mixed, 10 cases. In group 1, the sole lesion was in the right ventricle. Two cases were fresh, one old, and one case had both old and recent infarcts. Two were in the anterior apical area with extension into the anterior portion of the interventricular septum, one in the posterior-basal area with extension into the posterior portion of the interventricular septum, and one case in the posterior lateral region. In each case the main right coronary artery was involved. Group 2 included the cases in which the main area of infarct was

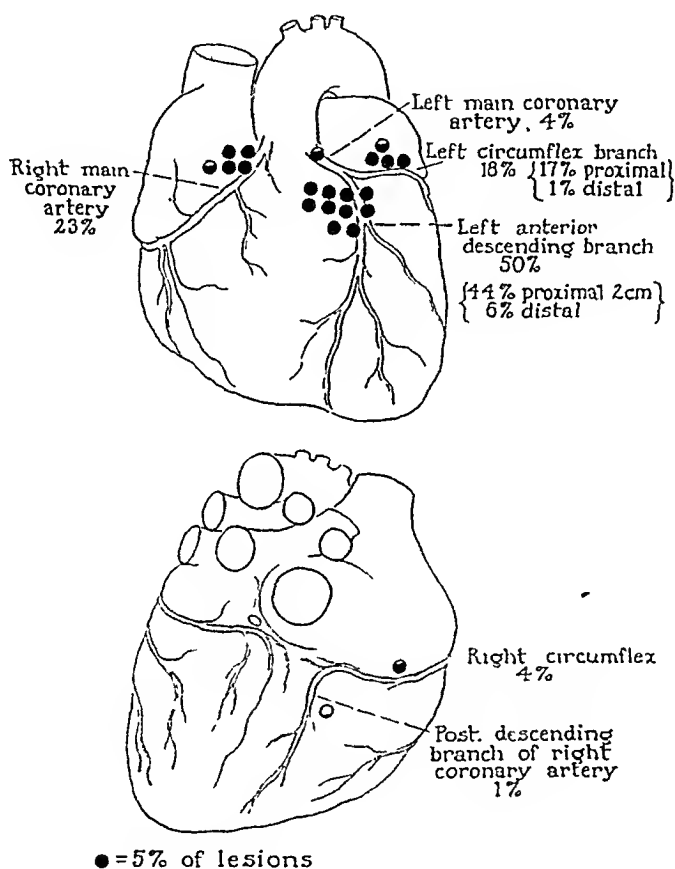


CHART 2. Sites of 207 occlusions in 132 cases of myocardial infarction.

in the left ventricle, and the contiguous adjacent right ventricle was involved for a distance of 0.5 to 2 cm. The distribution of the eight cases in which both ventricles were so involved was: five in the anterior apical portion and anterior interventricular septum, and three in the posterior basal portion. Six infarcts were new and two old. Group 3 consisted of 10 cases with both overflow and separate infarcts of the right ventricle; in other words, a combination of groups 1 and 2. In five cases the infarct in the right ventricle was the same age as the infarct in the left ventricle. The distribution of the separate infarcts was: five cases posterior basal, one anterior basal, two anterior apical, and two entire anterior surface. The right coronary artery

was occluded in each case, in addition to the occlusion of the afferent artery of the infarct in the left ventricle. In three cases, the right coronary artery was predominant, supplying the posterior surface of the left ventricle. There were old recanalized lesions in the right main coronary artery and old infarcts of the anterior right ventricle, and a recent thrombus in the distal portion of the right circumflex branch with a recent infarct of the posterior basal portion of the left ventricle.

Infarcts of the atria occurred 17 times (7.2 per cent), twice in the left and 15 times in the right chamber. Of the 17 cases, 13 showed other infarcts in the left ventricle of which 10 were in the anterior-apical and three in the anterior-apical and posterior-basal areas. In four cases only an atrial infarct was discovered. The incidence of atrial infarcts in this series is lower than that reported by Cushing, Feil, Stanton and Wartman² who found infarcts in the atria in 17 per cent of cases which had ventricular infarcts. This is probably due to the fact that atrial lesions were not specifically looked for in the early cases in the present series. The preponderance of infarcts in the right atrium which has been previously reported² was confirmed.

Site of Occlusion. Definite occlusions were found in the coronary arteries of 132 of 160 cases (82.5 per cent) of infarcts of the myocardium. These cases will be discussed first and the 28 cases in which occlusions were not found will be taken up later.

The various types of lesions which caused occlusion will be found in table 9 and have been discussed previously. Chart 2 shows the sites of 207 occlusions which were found in 132 hearts with infarcts. Eighty-eight per cent of the lesions occurred in the proximal parts of the main arteries, i.e.,

TABLE XV
Distribution of Arterial Occlusions in 132 Cases with Myocardial Infarcts

Artery	Number of Cases
Left anterior descending coronary artery	46
Left anterior descending, and right main	21
Right main	16
Left circumflex	13
Left circumflex and left anterior descending	13
Left circumflex and right main	4
Left circumflex, right main, and left anterior descending	4
Left main	1
Left main and left anterior descending	2
Left main, left anterior descending, left circumflex	1
Left main, left anterior descending, right main	1
Right circumflex	2
Right circumflex, left anterior descending	3
Right circumflex, left circumflex	1
Right circumflex, right main, left anterior descending	1
Right posterior descending	1
Right posterior descending, left circumflex	1
Right posterior descending, left circumflex, left anterior descending	1
Total	132

main left, proximal 4 cm. of the main right, proximal 2 cm. of left circumflex and left anterior descending artery. These data need no comment for they conform to the general experience.

Table 15 shows the various combinations of arterial occlusions. It is interesting to note that the right coronary artery, either alone or in combination with other arteries, was implicated in 35 per cent of all cases. Both main coronary arteries were occluded in 37 cases. Two major branches of the left coronary artery were occluded in 22 cases. Table 16

TABLE XVI
Comparison of Distribution of Arterial Occlusions by Per Cent of
Lesions and Per Cent of Cases

	Left Ant. Descending	Right Main	Left Circumflex	Right Post. Descend.	Left Main	Right Circumflex
Per cent lesions	50	23	18	1	4	4
Per cent cases	70	35	22	2	4	5

shows the distribution of arterial occlusions by per cent of lesions, and by per cent of cases. Fifty per cent of the lesions were in the left anterior descending artery, while 70 per cent of the cases had occlusion of this artery. The high incidence of multiple occlusions in several major coronary arteries (table 15) in the same patient explains this difference in percentage.

Correlation of the Sites of Coronary Occlusion and Myocardial Infarcts. Generally speaking, solitary occlusion of the anterior descending branch of the left coronary artery led to an infarct in the anterior-apical portion of the left ventricle and interventricular septum. There were 52 cases of this sort. In addition, there were 20 cases in which, despite occlusion of several arteries, the only infarct discovered was in the location just described. In nine of these cases the main right and the left descending coronary arteries were completely obstructed. It seems probable that there was predominance of the right coronary artery in these cases so that occlusion of this vessel resulted in an infarct at a distance. That is to say, there had been an old occlusion of the left descending coronary artery without resulting infarct, but when the main right coronary artery was occluded, then a fresh infarct, which was at a distance from the most recent obstruction, developed at the apex of the left ventricle. Infarcts of the apex of the heart were encountered with other combinations of occlusions such as all three main branches, and the descending and circumflex branches of the left coronary artery. In one case, there was occlusion of the main right coronary artery with infarction at a distance of the anterior-apical part of the left ventricle.

Solitary occlusion of the proximal circumflex branch of the left coronary artery resulted in infarcts in the posterior lateral portion of the left ventricle in four cases, and in the posterior basal area in nine cases. Nevertheless, the most common artery which was occluded in cases with posterior basal

infarcts of the left ventricle was the main right coronary artery (12 cases), indicating that in these hearts too, the right coronary artery was probably predominant. In several cases posterior basal infarcts of the left ventricle were found in hearts with multiple occlusions in the main right and left circumflex arteries.

Whenever an infarct was found in the right ventricle alone the main right coronary artery was occluded. When the anterior apical portion of the right ventricle was involved contiguously the descending branch of the left coronary artery was also occluded. All cases with infarcts in the posterior-lateral and posterior-basal areas of the right ventricle had occlusions in the main right coronary artery, and in several instances the circumflex branch of the left coronary artery was also involved.

Multiple infarcts of the anterior-apical and posterior-basal areas of the left ventricle had complete obstruction of both the descending branch of the left and the main right coronary arteries in 12 cases, and of the descending and circumflex branches of the left coronary artery in four cases.

At this point, it is appropriate to emphasize that, although an infarct is frequently found close to the occluded artery, which is usually the predominant artery for that area, this is not always true, and infarcts may be discovered at a distance from the affected artery.⁷ For this reason, it is preferable from the clinical viewpoint to diagnose the site of an infarct rather than the artery which is supposedly obstructed.

Coronary Occlusion in Cases of Myocardial Infarction. Complete occlusion, due either to thrombosis, embolism or arteriosclerosis, was found in 132 (82.5 per cent) cases of myocardial infarction. In another nine cases (5.6 per cent) there was coronary arteriosclerosis with stenosis of such marked degree as to account for the infarcts which were discovered in the left ventricle. An additional four cases (2.5 per cent) with stenosing arteriosclerosis had infarcts in the atria only. Cushing, Feil, Stanton and Wartman² have previously reported that in a high percentage of atrial infarcts an occlusion is not found. Small multiple infarcts were found in one case of polycythemia and in three cases of endocarditis lenta there were small mycotic infarcts.

Thus 11 cases (6.9 per cent) remained in which no occlusive lesion was discovered despite the presence of infarcts. Severe arteriolar sclerosis was noted in several cases, but in six cases (3.8 per cent) no explanation for the infarcts was found.

Myocardial Infarcts in Cases with Coronary Thrombosis. Myocardial infarcts were discovered in 84 per cent (119) of patients with coronary thrombosis (table 17), leaving 16 per cent (23) who died of coronary thrombosis without myocardial infarcts. Only three of these were hypertensive. Fourteen of the 23 patients died suddenly, within three hours of the earliest onset of clinical symptoms, before morphological infarcts could be expected to develop. Twelve were above 50 years of age, two between 40

and 50 years. Thirteen were males and one was a female. All were white. In the series of 160 cases the ratio of males to females was 1.9 to 1, and white to black 4 to 1. Every case of sudden death had generalized coronary arteriosclerosis with marked stenosis. Five cases had multiple recent and old occlusions of the major rami. The left coronary was involved in eight cases, the right coronary artery in six cases. Specifically the vessels involved were: left main and left anterior descending, three cases; left anterior descending, three cases; right main, three cases; right main, left anterior descending and left circumflex, one case; right circumflex and left anterior descending, one case; right circumflex, one case; left main, one case; and left circumflex, one case. A notation was made in several cases in which the occlusion was in the main right artery, that the greater part of the posterior

TABLE XVII

Incidence of Myocardial Infarcts in Cases with Coronary Thrombi

	Number of Cases	Per Cent of Cases
Thrombi with infarcts	119	84
With hypertensive heart disease	62	
With arteriosclerotic heart disease	54	
With rheumatic heart disease	3	
Thrombi without infarcts	23	16
With hypertensive heart disease	3	
With arteriosclerotic heart disease	20	
Total	142	100.0

surface of the heart was supplied by that artery, that is, the right coronary was predominant.

Sudden Death. In this study, the factors concerned in sudden death following coronary thrombosis were: (1) Severe generalized coronary arteriosclerosis; (2) multiple occlusions with involvement of the predominant artery; (3) males were more susceptible than females; (4) whites more than negroes; (5) age was apparently not an important factor.

Of the nine patients with thrombosis without infarction in whom sudden death did not occur, six had old thrombi without infarcts. Possibly a collateral circulation had prevented the development of infarcts. Three cases had recent thrombi which according to the clinical history were of two to three days' duration. All nine cases had marked generalized stenosing coronary arteriosclerosis. The distribution of lesions was as follows: In three cases the left anterior descending branch was involved, in three cases the right main coronary, in two the left circumflex, and in one case there was a recent occlusion of both left anterior descending and circumflex as well as an old one in the right main coronary artery. The causes of death in these nine cases were: pneumonia, four cases; pulmonary embolism, one case; peritonitis, two cases; and heart failure, two cases. The age distribution was similar to the group that died suddenly of coronary thrombosis. Eight were above 50 years of age and one was 42 years old.

To summarize the above, 16 per cent of cases with coronary thrombosis did not develop myocardial infarcts. Ten per cent died quickly before an infarct could reasonably be expected to develop. Since 58 per cent (93) of patients with myocardial infarcts were hypertensive, and only 13 per cent (3 of 23 cases) with coronary thrombosis but without myocardial infarcts were hypertensive, it appeared that arterial occlusion produced infarcts in hypertensives more readily than in non-hypertensives. Furthermore, coronary thrombosis caused sudden death more frequently in non-hypertensive patients. Thirteen of 14 patients (93 per cent) who died suddenly were non-hypertensive, whereas 42 per cent of the series was non-hypertensive.

ASSOCIATED CARDIAC LESIONS (COMPLICATIONS) IN MYOCARDIAL INFARCTION

The most common cardiac complications of myocardial infarction were: mural thrombi, subsequent infarcts, acute fibrinous pericarditis, aneurysm formation, and rupture of the heart.

Of 160 cases with myocardial infarcts, 40 per cent (64 cases) had *mural thrombi*. This incidence agrees with reports in the literature.¹ Of 94 cases with single myocardial infarcts 32 (34 per cent) had mural thrombi, of which 22 were fresh and 10 old. In 66 cases of multiple myocardial infarcts, 32 cases (48.5 per cent) had mural thrombi of which six had multiple old infarcts, three multiple recent, and 23 recent and old infarcts. Thus multiple repeated episodes of infarction seemed to increase the chances of mural thrombosis. The location of the intracardiac thrombi was always directly beneath the infarct. In 44 cases the thrombi were in the anterior portion of the left ventricle, in 10 cases in the posterior basal portion, in 14 cases in the right auricle, and in four cases in the right ventricle. In eight cases there were mural thrombi in both ventricle and auricle.

Subsequent Infarcts. The tendency for patients with one infarct to develop subsequent lesions is indicated by table 18. Fifty-one cases (32 per cent) had both fresh and old infarcts. In 10 cases there were multiple recent infarcts which were not all of the same age.

Acute fibrinous pericarditis was found in 31 of 111 cases (28 per cent) with recent myocardial infarcts and was localized over the myocardial lesion. Twenty-two (71 per cent) of these 31 cases also had mural thrombi. This common association of fibrinous pericarditis and mural thrombosis is not surprising when the anatomy of the heart muscle bundles is considered. The apex of the heart, which was the site of the infarct in over 66 per cent of all cases, is composed of two relatively thin layers of muscle, namely, the superficial sino-spiral and superficial bulbo-spiral muscles. These muscles make up the full thickness of the apical fourth of the left ventricle and twist around at the apex to pass upward and form the subendothelial surface and papillary muscles of the left ventricle.⁵ Infarcts in this area usually involve both superficial muscles and hence the entire thickness of the heart wall,

predisposing to both pericarditis and thrombosis. In a few cases pericarditis and mural thrombi were also found in the posterior basal portion of the left ventricle. Often the subepicardial and subendocardial muscle in this region were the seat of infarction, the middle layer of muscle being spared. This denoted involvement of the superficial bulbospiral muscle, part of which is superficial (subpericardial) and part deep (subendocardial). Mural thrombi were also common in cases with atrial infarcts. This is probably explained by the fact that the atria are composed of thin muscle bundles.⁵ Thus, patients with infarcts in the apex of the heart or in the atria may be expected to show thrombo-embolic phenomena. Fifty-five per cent of cases with intracardiac thrombi had occlusions of peripheral vessels from either thrombi or emboli. Thirty-nine per cent of cases without mural thrombi

TABLE XVIII

Chronology and Multiplicity of Myocardial Infarcts in 160 Cases

Number of Infarcts	Recent	Old	Recent and Old	Total Number of Cases
Single	50	44	—	94
Multiple	10	5	51	66
Total	60	49	51	160

had similar lesions. Emboli in the peripheral circulatory system with distant infarcts were a main or contributory cause of death in 43 of 160 patients (27 per cent).

Aneurysm formation occurred in 35 cases of myocardial infarcts. Cases with diffuse dilatation of the ventricle were not included, but only those with more or less well circumscribed dilatation involving the area of infarction. There was a higher incidence of aneurysm in cases with multiple infarcts (26 per cent) than in cases with single infarcts (19 per cent). Aneurysms developed progressively in the site of the infarct. This was shown by the fact that of 60 cases with a recent infarct, seven (12 per cent) had aneurysms; of 49 cases with an old infarct, 14 (29 per cent) had aneurysm, and of 51 cases of both recent and old infarcts 14 (28 per cent) had aneurysms. Mural thrombi and acute fibrinous pericarditis were a common accompaniment. Seventeen (49 per cent) of the 35 cases had mural thrombi and 10 (59 per cent) of the 17 cases had both mural thrombosis and pericarditis. Four (11 per cent) of the cases had pericarditis alone. The possible clinical significance of these observations are apparent: about half of the cases with myocardial aneurysm had mural thrombi. Seventy-one per cent of cases with myocardial aneurysm and pericarditis also had mural thrombi.

The aneurysms occurred in the same areas where infarcts were most frequent, i.e., 25 cases anterior apical, three cases posterior and lateral, and

seven cases posterior basal portion of the left ventricle. In three of the 25 cases of anterior apical infarction and aneurysm formation, the interventricular septum was also involved and bulged into the right ventricle. Rupture occurred in five of 35 cases (14.3 per cent) of cardiac aneurysm.

Cardiac Rupture. There were seven cases of cardiac rupture in the 160 cases of myocardial infarcts (4 per cent). Six of the 111 cases of recent infarcts ruptured at the site of the recent lesion; the other case occurred in an aneurysm in an old posterior basilar infarct of the left ventricle. Rupture occurred in the anterior wall of the left ventricle near the apex in four cases, and in three cases in the posterior basal portion of the left ventricle.

In this series rupture occurred at the site of an aneurysm in five of seven cases. In the cases of recent infarct, five ruptured from two to seven days, and one on the eighteenth day after the onset of clinical symptoms. Apparently the size of the infarct did not play a dominant rôle, since in only one case was the infarct massive. Lowe and Wartman⁵ have shown that both aneurysm and rupture are determined in large part by the number of muscle bundles which are involved. If an infarct involves the full thickness of the wall, that is, if two or more muscle bundles are affected, the muscle may break as soon as granulation tissue appears. However, if only a portion of the thickness of the wall is involved, as when a single bundle is necrotic, rupture occurs less and aneurysm more frequently. Increased intraventricular pressure, absolute or relative, probably plays a rôle also.⁸

MISCELLANEOUS

Syphilitic Heart Disease. This group consisted of 20 cases of syphilitic aortic valvulitis. There was syphilitic aortitis in all cases and aortic aneurysm in 11. The coronary ostia were stenotic in two cases. Heart failure caused death in 13 cases. The average weight of the heart in the entire group was 532 grams; of those who died in heart failure it was 626 grams; and of those who died of other causes 360 grams.

Cor Pulmonale. There were 18 cases with hypertrophy of the right ventricle. Associated pulmonary diseases included bronchiectasis, silicosis, chronic bronchitis, emphysema, and congenital cystic disease of the lungs. There was one case of enlargement of the right heart and failure secondary to marked kyphoscoliosis. The average heart weight was 420 grams. Two cases had systemic hypertension. Failure of the right side of the heart occurred in eight cases.

There were four cases of embolism into the right ventricle, resulting in acute cor pulmonale and sudden death. The right ventricle was dilated and distended by the coiled embolus. In two cases the embolus appeared to originate from pelvic veins, six and seven days after an operation; and in two cases from the site of fractures of the femur and pubis at the time of manipulation and reduction. However, the veins of the lower extremities were not regularly explored.

Pericarditis. This group included 32 cases of acute fibrinous and 20 cases of healed pericarditis. Pericarditis due to rheumatic heart disease or myocardial infarct was not included in this group, but in the respective groups. Twenty-five cases of fibrinous pericarditis due to uremia were included in the group "hypertensive heart disease."

Acute pericarditis, fibrinous, serofibrinous or fibrinopurulent, occurred secondary to the following diseases in this order of frequency: uremia, myocardial infarcts, rheumatic pancarditis, pneumonitis (lobar and bronchopneumonia), septicemia, and carcinoma of the lung.

There were 20 cases of chronic pericarditis of which five were constrictive. Two of the five were tuberculous in origin. Three had been surgically decompressed, of which one patient survived two years and died of other causes. Of the two cases which were not operated on, one died of cardiac insufficiency. The heart weight of 14 of the cases ranged between 250 and 350 grams. In six cases, the heart was enlarged with an average weight of 530 grams. There was associated hypertension in two cases, valvular deformity in one case, and mediastinal-diaphragmatic adhesions in three.

Cardiac Hypertrophy of Unknown Cause. This group included 16 cases of cardiac hypertrophy of unknown cause (non-hypertensive, non-arteriosclerotic, non-valvular). Three were children with hearts weighing 30 to 59 per cent above the expected weight (one leukemia, two pneumonia). The average weight of the 13 adult hearts was 440 grams.

Fat Infiltration. This group included 33 cases of moderate and marked fat infiltration of the heart without coronary artery or valvular disease. The ratio of females to males was 1.5 to 1 whereas the ratio of females to males in the whole autopsy group was 0.6 to 1, suggesting a greater incidence in females. No significant difference in heart weights existed in males and females, the average weight being 350 and 325 grams respectively. The average body weight of males was 59 kilograms, and of females 63 kilograms. Moderate fat infiltration occurred in some cases of severe emaciation. In one case there was slight cardiac decompensation.

Fatty Degeneration. Fatty degeneration occurred in 30 cases, three pernicious anemia, four myeloid leukemia, four uremia, eight carcinomatosis, two diabetes mellitus, five chronic pulmonary infections, and four chronically decompensated arteriosclerotic heart disease. In two cases, mild cardiac decompensation occurred in the absence of hypertension, coronary artery or valvular disease. However, not all hearts were stained for fat.

Atrophy of the Heart. Atrophy of the heart occurred in 19 cases, all of which had wasting diseases. Fourteen cases were secondary to widespread metastases (carcinoma of the stomach four, colon two, lung, liver, breast, esophagus each one case, and undetermined primary source four cases). Five cases occurred in chronic ulcerative pulmonary and peritoneal tuberculosis, Hodgkin's disease and Simmonds' disease. The hearts were uni-

formly small, with average weight of 198 grams, ranging from 140 to 240 grams. The muscle fibers were small, with droplets of brown pigment at the ends of nuclei. The subepicardial fat was sparse and the seat of serous atrophy. The coronary arteries were tortuous, owing to shrinkage of the myocardium. In only one case was there systemic hypertension, 150 mm. mercury systolic and 100 mm. diastolic, and the heart weighed 210 grams.

Myocarditis. This group included 16 cases of acute, 14 subacute, and three chronic myocarditis. The 16 cases of acute myocarditis consisted of 10 cases of acute diffuse, two of acute focal, three of acute interstitial, and one of acute suppurative myocarditis. The average weight of the heart in acute interstitial myocarditis was 290 grams. Acute diffuse myocarditis occurred in three cases of pneumonia, in three cases of septicemia due to erysipelas, infected abortion and impetigo, in two cases of brain tumor, in two cases of pulmonary and intestinal tuberculosis. There were two cases of focal myocarditis of the right ventricle in pneumonia, and atrophic arthritis. Suppurative myocarditis was found postoperatively after decompression of a patient with constrictive pericarditis. Subsequent rupture of the heart caused death.

Subacute myocarditis occurred in 14 cases; seven cases had acute infections, pneumonia, suppurative otitis media and mastoiditis; one case occurred in each of the following: uremia, acute hepatic necrosis, intestinal obstruction, myasthenia gravis, carcinoma of the stomach, cirrhosis of the liver, and cause unknown. The process was focal in the right ventricle in three cases.

The three cases of chronic myocarditis occurred in uremia, tuberculosis of the spine and meningococcemia.

Neoplasm of the Heart. Sixteen cases had neoplasms of the heart, of which one was a primary leiomyosarcoma of the right atrium with direct extension into the superior vena cava, left subclavian vein, and myocardium of the right ventricle and left atrium. Metastases were found in lungs and adrenals.

Primary tumors which metastasized to the heart were: lung six cases, pancreas three cases, stomach two cases, lymphoblastoma three cases, breast one case. The tumors were all poorly differentiated. The visceral and parietal pericardia were involved in 10 cases, and pericardium, endocardium and myocardium in five cases. Cardiac symptoms due to tumor metastases occurred in four cases. Antemortem diagnosis of tumor metastasis to the heart was made in one case. In one case of carcinoma simplex of the lung, metastases to the posterior portion of the left ventricle caused symptoms of infarction and electrocardiographic changes suggestive of a posterior basal infarct. In a case of squamous cell carcinoma of the right bronchus, rupture of the right ventricle occurred at the site of metastases.

Valvulitis (Non-Rheumatic). This group included 10 cases of acute bacterial endocarditis, 12 cases of thromboendocarditis and 17 of chronic non-rheumatic valvulitis.

Acute Vegetative and Ulcerative Bacterial Endocarditis. The bacteria responsible in five cases were pneumococci, one case *Streptococcus viridans*, and four cases undetermined. Five cases had lobar pneumonia, three cases septicemia originating in osteomyelitis of the frontal sinuses and sacrum, one case from secondarily infected carcinoma of the colon, and in one case the site was undetermined. The aortic valve was involved in seven cases, the mitral in three, the tricuspid in two and the left atrial endocardium in one case. In three cases acute bacterial endocarditis occurred in the aortic valve of a heart with healed non-deforming endocarditis of the mitral, aortic and tricuspid valves. In one case an aortic leaflet ruptured.

Thromboendocarditis occurred in 12 cases, seven non-rheumatic verrucous endocarditis, three endocarditis minima, two atypical verrucous endocarditis. The valves were involved in the order mitral seven cases, aortic six, tricuspid one, pulmonic one.

Chronic Non-Rheumatic Valvulitis. In 14 cases there was healed non-deforming endocarditis involving mitral, aortic and tricuspid valves in that order of frequency. In three cases there was in addition calcific aortic stenosis. It is possible that stigmata of associated rheumatic disease would be found upon reexamination of these cases.^{12, 4}

Air embolism occurred during an operation on a tumor of the neck involving the right subclavian vein and resulted in immediate death.

Trauma. Contusion of the heart occurred in a graze bullet wound, and chest injury. In both cases death was due to cardiac decompensation.

SUMMARY

The protocols of 2,000 consecutive autopsies performed at the Institute of Pathology, Western Reserve University, from 1935 to 1940, were reviewed in order to determine the incidence of the various diseases of the heart. Eighty per cent were white, and 20 per cent negro; 64 per cent males and 36 per cent females. The age curve of this series was similar to that of deaths from all causes in the United States Registration Area for 1940. Forty-nine and two tenths per cent of the patients had some cardiac lesion at autopsy, although not all were sufficiently important to have contributed to death. Nineteen per cent of the total autopsy population died directly of heart failure.

The cardiac lesions were divided into four main groups: rheumatic heart disease, hypertensive heart disease, coronary artery disease, and a miscellaneous group. Thirteen and six tenths per cent of the autopsy group had hypertensive heart disease. The chance of dying in heart failure was not increased by hypertension for patients with coronary arteriosclerosis, occlusions and infarcts.

The age, sex, color distribution of 120 cases of rheumatic heart disease was presented. The mitral valve was involved in every case, and aortic in 85, the tricuspid in 53 and the pulmonic in 15. Forty-nine (41 per cent)

cases of rheumatic carditis lived to be 45 years old or more. There were 16 cases of endocarditis lenta among the 120 cases of rheumatic heart disease (13 per cent).

The coronary arteries were significantly diseased in 51 per cent of the 984 cases with heart lesions, or 25 per cent of the total autopsy series. The heart was enlarged in 69 per cent of cases with coronary artery disease. The importance of arteriosclerosis, thrombosis and intramural hemorrhage in producing occlusion of the coronary arteries is discussed. Eighty-four per cent of the lesions occurred in the proximal parts of the main arteries. Multiple occlusions were found in many cases. The right coronary artery was implicated in 35 per cent; the left anterior descending artery in 70 per cent of all cases. Eighty-four per cent of cases with coronary thrombosis also had myocardial infarcts, 16 per cent died without myocardial infarcts, many of them suddenly, within three hours of the earliest onset of clinical symptoms and before morphological infarcts developed. The factors concerned in sudden death following coronary obstruction were severe generalized coronary arteriosclerosis, and multiple occlusions with occlusion of the predominant artery. Age was apparently not an important factor.

The incidence of myocardial infarcts in the total autopsy series was 8.2 per cent. The pertinent data were analyzed as to incidence, etiology of occlusions, location of infarcts, site of occlusion, correlation of occlusion and infarcts, and associated lesions in the heart. Single infarcts were more common in men than women; multiple infarcts were proportionately more common in women than men; infarcts were relatively more common in colored than white women; fewer infarcts were found in negroes than would be expected from the race incidence. The left ventricle was the most frequent site of an infarct; infarcts were also found in the right ventricle, and both atria. The problem of infarction at a distance is discussed.

The most common cardiac complications of myocardial infarction were mural thrombi (40 per cent), fibrinous pericarditis (28 per cent of recent myocardial infarcts), subsequent myocardial infarcts (32 per cent), aneurysm formation (22 per cent), and cardiac rupture (4 per cent). Peripheral thrombo-embolism occurred in 45 per cent of cases of myocardial infarcts, and were a main or contributory cause of death in 43 of 160 cases.

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RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE OF RECENT YEARS

(Ninth Rheumatism Review) *

Part I

By PHILIP S. HENCH, M.D., F.A.C.P., *Rochester, Minnesota*
(Chairman, Editorial Committee),
WALTER BAUER, M.D., F.A.C.P., *Boston*,
EDWARD W. BOLAND, M.D., *Los Angeles*,
DARRELL C. CRAIN, M.D., F.A.C.P., *Washington, D. C.*,
RICHARD H. FREYBERG, M.D., F.A.C.P., *New York*,
WALLACE GRAHAM, M.D., F.R.C.P. (C), *Toronto*,
W. PAUL HOLBROOK, M.D., F.A.C.P., *Tucson, Arizona*,
L. MAXWELL LOCKIE, M.D., F.A.C.P., *Buffalo, New York*,
CURRIER MCEWEN, M.D., F.A.C.P., *New York*,
EDWARD F. ROSENBERG, M.D., F.A.C.P., *Chicago*,
ROBERT M. STECHER, M.D., F.A.C.P., *Cleveland*

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The last Review prepared by the Editorial Committee of the American Rheumatism Association was the Eighth; it concerned the American and English literature for 1940 and was published in the *Annals of Internal Medicine*, Volume 15, December, 1941. This Ninth Review, begun in 1941, was interrupted by the war as most of the Committee entered military service. This Review has been prepared and published under difficulties. Regrettably it was impossible to include the literature of 1946 because the *Quarterly Cumulative Index Medicus* for 1946 had not yet appeared when the contents of this review had to be determined. The editorial comments express the opinions of the authors of the Review, the Editorial Committee, and are not necessarily those of the Association.

DEFINITION OF "RHEUMATISM" AND THE "RHEUMATIC DISEASES"

UNSATISFACTORY as they are, the terms "rheumatism" and "rheumatic diseases" remain the best under which to group illnesses characterized by pain and stiffness of joints, muscles and related structures. In Europe "acute rheumatism" usually refers to rheumatic fever.^{1215, 1831} Derivation of terminology was discussed by Edgecombe. An interesting historical note on "arthritis through the ages" was published by Burbank.

GENERAL INCIDENCE OF RHEUMATIC DISEASES:
SOCIAL AND ECONOMIC IMPORTANCE

The great responsibility of the medical profession and laymen to the problems of rheumatism was again emphasized in the Association's revised "Primer on arthritis."³⁶² In the United States, rheumatism heads the list of specified chronic diseases. Disability from rheumatic diseases exceeds that from tuberculosis by a ratio of 10:1, that from diabetes by nearly 10:1, that from cancer and tumor by 7:1. England and Wales have more than 1,000,000 adult sufferers from rheumatism yearly.¹²¹⁵ Among 1,800,000 medically insured persons in Scotland, during a five-year period ending in 1938, rheumatism caused 3,000,000 days of incapacity and 45,300 new cases of disability, mostly certified as "muscular rheumatism." When "articular rheumatism" was present, the incapacity was prolonged.¹²¹⁵

American and foreign reports reveal a growing appreciation of the social and economic importance of rheumatism. In the United States rheumatism has annually invalidated 147,000 persons, has cost 97,000,000 days lost from work, \$200,000,000 in wages and more than \$100,000,000 for medical care.^{362, 1157}

In the British Isles, a sixth of the total absenteeism due to sickness is attributable to rheumatic diseases: "The time lost by reason of chronic rheumatism is equal to having an army of 60,000 people off work all the year round" (Underwood). "Chronic rheumatic joint disease" costs Great Britain 20,000,000 to 25,000,000 pounds annually.^{523, 864} Rheumatism is one of the most important unsolved medical problems in the British Isles, according to Horder.^{526c} In Scotland about 335,000 new cases of rheumatic disease are reported yearly. More than a fourth (27 per cent) of the prolonged absences from school were due to rheumatic diseases as compared to 7 per cent from tuberculosis. "There are at least 200,000 child sufferers from 'rheumatism' in the Kingdom" (Horder).⁸⁶⁴

In Sweden a twenty-fifth of the population suffers from rheumatic disease, according to a recent survey.³⁸¹ Of Sweden's population of 6,500,000 persons, 100,000 were permanently incapacitated despite the fact that arrangements for treating rheumatism in Sweden are probably the best in Europe. In Sweden 9 per cent of the total pensionable invalidity is due to rheumatism¹⁸³¹; between 40,000 and 50,000 persons received premature pensions in 1942 because of rheumatic diseases and there were 70,000 pensioned rheumatics.¹⁷⁴⁷

According to Horder⁸⁶⁶ the contingencies of war, which subjected civilians and military personnel to inclement weather, to manual labor to which many were unaccustomed, and to nutritional deficiencies and psychic shock, increased the incidence of rheumatism.

CLASSIFICATION OF DISEASES OF JOINTS AND RELATED STRUCTURES

If the etiology of the various rheumatic diseases were known, their classification would be simplified. Meanwhile some physicians merely consider rheumatism as articular or nonarticular, acute or chronic. Others divide the arthritides into (1) those of known etiology and (2) those of unknown etiology.¹¹⁵⁷ Several classifications based on clinical features recently appeared.^{173, 271, 504, 523, 570, 727, 740, 864, 1798, 1937} The inclusive classification recently prepared by the New York Rheumatism Association follows¹⁷⁴⁵:

- A. Infectional arthritis of proved etiology
- B. Probably infectional; etiology unproved
 - 1. Arthritis of rheumatic fever
 - 2. Rheumatoid arthritis (atrophic, chronic infectious)
 - (a) Adult type
 - (b) Juvenile type (Still's disease)
 - (c) Ankylosing spondylitis (Marie-Strümpell, etc.)
 - (d) Psoriatic arthritis
 - 3. Arthritis associated with various infections
- C. Degenerative joint disease
 - 1. Osteoarthritis (hypertrophic, degenerative)
 - (a) Generalized
 - (b) Localized
 - (1) Secondary to previous trauma
 - (2) Secondary to structural abnormality
 - (3) Secondary to previous infectional arthritis
 - (4) Cause unknown
- D. Arthritis associated with disturbance of metabolism
 - 1. Gout
 - 2. Others
- E. Arthritis of neuropathic origin
 - 1. Secondary to tabes dorsalis
 - 2. Secondary to syringomyelia
- F. Neoplasms of joints: cyst, xanthoma, hemangioma, giant-celled tumors, synovioma
- G. Mechanical derangements of joints
 - 1. Traumatic arthritis
 - 2. Joint disturbance secondary to abnormal postural strain
- H. Miscellaneous forms
 - 1. Manifestations of systemic disease
 - (a) Arthritis of serum sickness
 - (b) Arthritis of hemophilia
 - (c) Intermittent hydrarthrosis
 - (d) Pulmonary osteo-arthropathy
 - (e) Hysterical joints
 - 2. Local joint disturbances
 - (a) Aseptic bone necrosis
 - (1) Secondary to contusion, fracture, dislocation or air embolism
 - (2) Of unknown etiology (juvenile osteochondritis, Legg-Calvé-Perthes' disease, Kohler's disease, Freiberg's disease, Osgood-Schlatter's disease)
 - (b) Osteochondritis dissecans
 - (c) Osteochondromatosis

Excellent criteria for diagnosis of these various types of arthritis are appended to this classification.

The 1942 "Primer on arthritis"³⁸² listed five main groups of arthritis: (1) proved infectious, (2) probably infectious, etiology unknown, (3) degenerative joint disease, (4) resulting from physical trauma, and (5) gouty arthritis.

The classification recently approved by the American Rheumatism Association for inclusion in the "Standard Nomenclature of Disease" follows:

1. Arthritis due to specific infection. *Specify organism when known.*
2. Arthritis due to rheumatic fever.
3. Arthritis, rheumatoid. *Specify as multiple or of spine.*
4. Degenerative joint disease, multiple due to unknown cause; osteoarthritis.
5. Arthritis due to direct trauma.
6. Arthritis due to gout.
7. Neurogenic arthropathy.
8. New growths of joints.
9. Hydrarthrosis, intermittent.
10. Periarticular fibrositis.
11. Diseases in which arthritis, arthropathy or arthralgia is frequently associated (diagnose disease, list joint manifestation as symptom):

Acromegaly	Osteochondritis dissecans
Acute disseminated lupus erythematosus	Osteochondromatosis
Cyst of meniscus of knee	Periarteritis nodosa
Dermatomyositis	Psoriasis
Drug intoxication. <i>Specify.</i>	Pulmonary osteo-arthropathy
Erythema multiforme exudativum	Purpura, various types
Erythema nodosum	Raynaud's disease
Hemophilia	Reiter's disease
Hysteria	Scleroderma
Ochronosis	Serum sickness

[For the sake of simplification, clarity and unification of terminology it is suggested that this classification of the American Rheumatism Association be adopted throughout the United States.—Ed.]

RELATIVE FREQUENCY OF THE RHEUMATIC DISEASES

Among 48,000 people in Sweden, a recent survey showed 2.4 per cent had, or had had rheumatic fever; 2 per cent rheumatoid arthritis; 1 per cent osteoarthritis, and 2.6 per cent sciatica (Copeman).³⁸¹ [This was a small sample of the population; other forms of rheumatism were not mentioned, hence this survey may not have indicated accurately the relative incidence in Sweden.—Ed.] The distribution of different types of rheumatism among 1,000 civilian cases of "chronic rheumatic diseases" in London was determined by Fletcher and Lewis-Fanning. There were 254 instances of "infective arthritis" [rheumatoid arthritis?—Ed.], 53 of "spondylitis ankylopoietica," 253 of osteoarthritis (not of spine), 44 of *malum coxae senilis*, 40 of gout, 114 of fibrositis, 10 of rheumatic fever and the remainder (232 cases) of miscellaneous types.

Interesting reports on types of rheumatic disease among soldiers in the recent war appeared. In a west coast United States Army General Hospital during 1942, 11 per cent of total admissions to the medical service were for rheumatic disease. Of 350

cases studied by Boland peripheral joints were affected in 214 (61 per cent); the remainder had "back complaints." Among the 214 patients with peripheral joints affected the relative incidences were as follows (in percentages): psychogenic rheumatism in 21; rheumatoid arthritis in 19; osteoarthritis in 16; acute rheumatic fever in 16; "arthritis unclassified" in 14; primary intramuscular or periarticular fibrositis in 5; gonorrheal arthritis in 2; gouty arthritis in 1 and miscellaneous articular conditions in 6. Later Boland and Corr at the same hospital found the relative incidence of "back complaints" among soldiers to be as follows (percentages): unstable backs 33; rheumatoid spondylitis 18; psychogenic rheumatism 18; spinal osteoarthritis 10; primary fibrositis 7; osteochondritis juvenilis dorsi 7; ruptured intervertebral disk 7.

The high incidence of psychogenic rheumatism in these series will be noted. In addition to the patients whose primary complaints were from psychogenic rheumatism, 13 per cent more had various organic rheumatic conditions with marked functional overlay—secondary psychogenic rheumatism.

The relative incidence among these American troops can be compared to that among 270 rheumatic British soldiers studied by Savage¹⁵⁴¹: 52 per cent had "fibrositis"; 15 postural backache; 9 sciatica; 9 osteoarthritis; 5 rheumatoid spondylitis; only 2 rheumatoid arthritis of peripheral joints; 1 rheumatic fever, and 7 per cent miscellaneous conditions.

Of the rheumatic diseases in a Scottish Army depot (World War II) 70 per cent were "muscular," 20 per cent "neuritic" and 10 per cent articular rheumatism.¹²¹⁵ Among 775 rheumatic English soldiers in the Middle East (World War II) 33 per cent had muscular fibrositis, 32 per cent had acute arthritis, 21 per cent had chronic arthritis and 14 per cent had sciatic pain (Kersley).⁹⁸⁹

[In another series of rheumatic British soldiers studied by Copeman,¹¹ 70 per cent had fibrositis, only 6 per cent had rheumatoid arthritis; psychogenic rheumatism was not mentioned as having been included or excluded. The supposed great frequency of "fibrositis," the relative rarity of rheumatoid arthritis and the infrequency or absence of primary psychogenic rheumatism among British troops is in sharp contrast to the relatively high incidence of *primary* psychogenic rheumatism and low incidence of fibrositis among American soldiers as reported not only by Boland but more recently by other American medical officers. These striking differences may be due, at least in part, to the fact that American medical officers who were trained in rheumatology set up diagnostic criteria whereby fibrositis and psychogenic rheumatism could be differentiated more confidently.⁸¹⁰ Whenever such a differentiation was not attempted most if not all of the cases of psychogenic rheumatism were probably catalogued as "fibrositis."—Ed.]

DISEASES OF JOINTS RELATED PRIMARILY TO TRAUMA

Types of Trauma. Joints can be damaged (1) by acute single injury or (2) by chronic injuries from minor, repeated trauma or microtrauma. "Microtrauma is the result of minute force applied internally or externally so that no lesion such as hemorrhage, exudation, destruction of cells or necrosis is immediately evident" (Duschak). The sensory response is below the threshold of perception or exceeds it only slightly. Acute injuries may produce lesions of ligaments or cartilage, symptoms of which are long delayed and the presence of which later produces chronic, sometimes progressive (secondary), traumatic arthritis.¹²¹

Lesions Produced by Acute Trauma. These may be varied and should not be lumped thoughtlessly under a single term, "traumatic arthritis." Ligaments or capsule may be stretched, lacerated or ruptured. Synovial membrane may escape injury or traumatic synovitis may develop. In knees menisci may be displaced, detached or torn. Articular cartilage may escape damage or may be

compressed, split or detached from subchondral bone. Juxta-articular bursae may be the main or only site of trouble. In severe injuries a joint may be dislocated or a bone fractured (Bennett).¹²¹

The knee is the commonest site of traumatic lesions because (1) it is a mechanically weak joint and (2) it, more than any other, is subject to "a multitude of severe or trivial injuries."¹¹⁸⁰

Traumatic Synovitis. Although injuries rarely affect synovia alone, a direct blow or contusion occasionally produces "simple traumatic synovitis," generally with hemorrhagic effusion.¹¹⁸⁰ In mild cases compression bandages and restricted activities are all that are required. Cold compresses are preferred to hot applications.⁶⁶ Recovery is complete in two or three weeks. Aspirations may be required when hemorrhagic effusions are marked. If synovitis becomes recurrent, suspect internal derangement.⁶⁶ In four cases of traumatic hyarthrosis Pelter¹³⁰¹ "reduced rapidly" the effusions by the oral use of ammonium chloride and a low salt, acid-producing diet. [The number of patients treated is too small to permit conclusions concerning such treatment.—Ed.]

Hemarthrosis. In joints severely injured hemarthrosis usually occurs and was present in 93 per cent of Mauck's 416 cases of injured knees. When swelling occurs immediately after trauma, it is almost always due to hemarthrosis. But hemorrhage into joints may occur without severe trauma.^{66, 1359} In any event articular distention from such effusions (especially into knees) is a prime factor in preventing healing of ligaments and cartilage, and is one of the greatest factors in producing an unstable joint, hypermobile cartilages and subsequent locking and damage.¹¹⁸⁰

Lipohemarthrosis. Hemorrhagic fluid is roentgenographically homogeneous. If free fat is also present, the fluid is not of homogeneous density but tends to separate into layers. In eight cases of injury to knees Peirce and Eaglesham noted in lateral roentgenograms "fluid levels of differential roentgenographic density" providing evidence of injury to juxta-articular fat, particularly in subpatellar fat pad and at the base of cruciate spines. Juxta-articular fat, even the subpatellar fat pad, is outside the synovial membrane although it is within the joint capsule. Therefore, when "traumatic lipohemarthrosis" is present one may assume that, due to severe injury, fat has been extravasated from one or more of the fat depots and also that the synovial lining has been torn. [Roentgenographic changes described in this interesting paper were quite clear. This report confirms that of Holmgren (1942).—Ed.]

Acute Traumatic Arthritis. In less severe cases pain, tenderness and effusion may disappear soon with healing and no residues. Sometimes articular hyaline cartilage is damaged but produces no early signs or symptoms because it is avascular and has no nerve supply. Due to its limited regenerative capacity cartilage heals slowly. Repeated roentgenographic examinations help to determine whether a progressive articular lesion has resulted from the initial trauma (Bennett).¹²¹

Late (Secondary) Traumatic Osteoarthritis. When articular cartilage is cracked or its surface damaged sufficiently to cause a scar, reaction about this damaged site from repeated motion and use in time may produce enough excess osteoid and scar tissue to make the joint function abnormally with the eventual production of late secondary traumatic osteoarthritis. In the hip the round ligament especially may gradually become scarred and enlarged; the excess tissue initiates maladjustment of articular surfaces which, if long continuing, produces hypertrophic changes (Ghormley).⁶³⁹

In knees, unhealed intrinsic lesions commonly produce such late osteoarthritis; degeneration of articular cartilage is hastened by overweight, overuse or the continued presence of loose bodies (Moorhead and Lyall).

In shoulders of professional baseball pitchers osseous deposits "strikingly similar to osteoarthritis" often develop on the posterior inferior border of the glenoid fossa. These exostoses irritate the circumflex nerve and pain is referred to the deltoid region. Such lesions in the posterior part of the shoulder are those which (in contrast to the less disabling lesions of the anterior part) may shorten a pitcher's career. A special roentgenographic technic to reveal the exostoses and the surgical procedure for their removal was described by Bennett¹²³ who also discussed occupational osteoarthritis and osteochondritis in elbows of pitchers. Surgical removal of loose bodies often relieved symptoms and restored full function.

The continued use of pneumatic tools for drilling and so forth occasionally produces unilateral sequelae: in wrists osteophytes at head of radius and at first carpometacarpal joint, osteochondritis dissecans especially of lunate or navicular bone, "spiking" of os trapezium, small areas of osseous decalcification; in elbows osteoarthritis, osteochondritis or periosteal proliferation ("olecranon spurs"); rarely in upper part of arm, myositis ossificans, or osteoarthritis of shoulder joint and calcific bursitis or both (Copeman).³⁷⁴

The superimposed weight of a normal man weighing 75 kg. (165 pounds) while standing or walking does not affect bone but does affect compressible soft interposed parts (articular cartilages, menisci, intervertebral disks). When weight rests on one leg the tibial condyle bears, according to Duschak, about 90 per cent of the body weight, in this case about 70 kg., a pressure of about 2 kg. per square centimeter of articular surface or 2 atmospheres of pressure. This is nearly 12 times that exerted by the normal systolic blood pressure (only 0.17 kg. per square centimeter). Thus, as long as body weight rests on the leg the circulation of tissue fluid within avascular cartilage stops completely (circulatory intermission, "rheopause"). Since this rheopause is normally short, cartilage remains unharmed under physiologic conditions. During weight-bearing a hip bears about 40 kg., the pressure being 1.55 kg. per square centimeter or nine times the blood pressure. Intervertebral disks below and above the fifth lumbar vertebra bear about half the bodily weight or 35 kg., 1.4 kg. per square centimeter or eight times the blood pressure. The disk below the fourth cervical vertebra bears 4 kg., 1 kg. of pressure per square centimeter or six times the blood pressure.

Under normal conditions no disordered local metabolism arises but during prolonged standing as in certain occupations the local circulatory intermission is lengthened; the flow of tissue fluids stops for a longer period. Despite its low metabolism articular cartilage is damageable. When rheopause exceeds a certain duration, an automatic defense in the form of "corrective unrest" occurs (unpleasant pressures, unrest, slight pains and stiffness) which forces a change of position. "Prolonged rheopause means malnutrition of cartilage, accumulation of waste products and stimulation of new formation of functionally inferior connective tissue with reduction of elastic fibers (fibrillation)."

Premature degenerative osteoarthritis may result especially in policemen, soldiers, salesmen, cooks, waiters, factory workers, housewives, nurses, dentists, surgeons and others whose occupations require long standing. Measures to prevent or lessen the results of such static microtrauma include shortening of the rheopause by brief interruptions of weight-bearing, by intercalated suitable motions or exercises, active hyperemia to improve blood supply, reduction of venous congestion by exercises, massage, elastic bandages and treatment of varicose veins and correction of obesity and static deformities (pronated feet, knock knees, bow legs, kyphosis) (Duschak).

Osteoarthritis of Temporomandibular Joint. This may result from acute or chronic exogenous trauma or from increased laxity of ligaments and resultant chronic mild subluxation.^{96, 289, 1203, 1558, 1588, 1600, 1848, 1931} Symptoms in one case

were relieved by surgical excision of the condylar tip.¹²⁰³ A new "simple and safe" treatment was used in 180 cases by Schultz and Shriner: repeated intra-articular injections of a sclerosing solution (sodium psyllate). The resulting mild fibrosis reportedly relieved symptoms in most cases.

Osteoarthritis of Patella. This may be associated with intrinsic lesions within the knee joint or may result from direct injury to the patella. The patella may become fixed to femoral condyles with marked limitations of motion. Patellar cartilage may become degenerated with the formation of a "squeaky knee." An offending patella may gouge deep grooves on the femoral surface. Secondary osteoarthritis of knee joint may ensue. In a few cases patellectomy was performed^{66, 1261, 1281} with relief of pain and increased mobility of knee.

Internal Derangements of Knee. Various internal derangements including those encountered by soldiers¹⁰⁰⁰ and by football players¹³³⁷ were discussed.

According to Mauck the primary damage is usually to ligamentous structures; medial collateral and crucial ligaments are most often damaged. Damage to semilunar cartilages is secondary. The more vulnerable medial meniscus is injured more often than the lateral.

The term "locking" received different interpretations. According to Levinthal¹⁰⁸³ "by locking we do not mean complete immobility." But Moorhead and Lyall¹²⁰¹ wrote: "Locking is often used to describe difficult extension of the knee due to pain, whereas actually it should mean an insurmountable wedging of the joint. This is a very important distinction."

All internal derangements are accompanied by a varying degree of synovial hyperemia and effusion. If the irritating body is not removed, this membrane becomes permanently thickened and irregular with the late formation of hypertrophic or villous synovitis.¹²⁶¹ Four cases of traumatic semimembranosus bursitis with tear of an internal meniscus, "an association not recorded in the literature," were noted by Burman.

The value of pneumoradiography (air arthrography) in the diagnosis of internal derangements was stressed and new technics were described.^{161, 298, 414, 765, 795, 1075} Thus, calcified menisci were differentiated from calcified loose bodies or calcified articular cartilage.

The usual remedies were discussed.^{66, 1000, 1083, 1180, 1261, 1337} A new plastic and steel knee brace weighing only 18 ounces (0.55 kg.) was demonstrated (Palmer).¹³³⁷ Conservative treatment should be employed first (temporary splinting, early weight-bearing, quadriceps exercises). When such measures fail surgical treatment is indicated, but should be done before irreversible secondary articular damage has occurred.

Sprains and Strains. The use of local anesthetics for sprains and strains was recommended. Often the part is "immediately restored to function" (Leinwand). Some used 2 per cent procaine hydrochloride.¹⁰⁷⁶ Others considered surface anesthesia by procaine iontophoresis as effective and more advantageous than the use of ethyl chloride spray^{400, 1034} or injection of procaine.¹⁰⁵⁷

Epicondylitis: Traumatic Radioulnar Synovitis ("Tennis Elbow"). The terms "epicondylitis" and "tennis elbow" are inadequate and misleading because the condition is noted not only in sports but in industrial injuries (Allen).¹⁸ Part of the disability results from nipping of the synovia of the radioulnar joint. In obstinate cases the enlarged synovial fringe should be excised.

SECONDARY INFLUENCE OF TRAUMA ON ARTICULAR DISEASES

Many articular diseases not primarily related to trauma (for example, rheumatoid arthritis, gouty arthritis, primary idiopathic senile osteoarthritis, neuroarthropathies) are notably influenced or modified by trauma of various sorts. The interrelationships were discussed.^{121, 1521}

GONORRHEAL ARTHRITIS AND GONORRHEAL "RHEUMATISM"

Incidence. Despite a high annual incidence of 1,000,000 or more cases of gonorrhea,¹⁰⁹² that of gonorrheal arthritis has decreased markedly.

In the presulfonamide era arthritis complicated 1 to 5 per cent of cases of gonorrheal urethritis; in Germany during World War I it complicated 10 per cent of cases of gonorrhea.⁷⁵⁹ Recently the incidence has fallen to between 0.1 and 0.3 per cent (Turner and Sternberg). In recent literature few reports dealt solely with gonorrheal arthritis. Harkness discussed 336 cases; Davis 16 more. Among many reports on gonorrhea only 70 additional cases of gonorrheal arthritis were mentioned in sufficient detail for independent appraisal, and since gonococci were usually not found in synovial fluid, most of the cases were of presumptive, not proved, gonorrheal arthritis.^{102, 413, 478, 580, 754, 831, 928, 1009, 1146, 1249, 1545, 1656, 1717, 1790, 1846, 1847} A few other cases of "arthritis" with gonorrhea were mentioned without any clinical details or results of treatment.^{147, 350, 703, 1788}

Clinical Data. Polyarthritis occurred in 83 per cent of Harkness' 336 cases of gonorrheal arthritis. The arthritis began an average of 43 days after the onset of urethritis. [This average seems to us unduly long. Could some of these cases have been, not of gonorrheal arthritis, but of "postgonorrheal rheumatoid arthritis"?—Ed.] Most often affected were knees (74 per cent), ankles (56 per cent), feet (32 per cent) and wrists (16 per cent). Talalgia (periostitis of os calcis) affected 6 per cent. Sternoclavicular joints were affected in 1.4 per cent, temporomandibular and intervertebral joints each in 0.6 per cent.

"Metastatic catarrhal conjunctivitis," different from gonococcal ophthalmia in that no gonococci were found in smears or cultures, was a complication in 10 per cent of Gabe's 100 cases of gonococcal arthritis from which, incidentally, "septuagenarians are not exempt."

Pathology and Roentgenography. No new data appeared.

Laboratory Data. Cultures of gonococci are the most reliable method of diagnosis.

Culture media recommended were Difco Proteose Peptone no. 3 Agar enriched with 2 per cent hemoglobin¹⁵⁸³ or with 12 per cent horse blood.¹⁷⁸⁸ Sugar fermentation tests may be used to confirm positive cultures. Three negative cultures within four weeks were considered a minimal criterion of cure.

Gonococcal fixation tests are of doubtful value¹⁷⁸⁷; results were positive in 77 per cent of Harkness' 336 cases of gonorrheal arthritis. Such tests may remain positive for as long as 50 years after the initial genital infection and a condition diagnosed gonorrheal arthritis 10 to 20 years after gonorrhea is "invariably not gonococcic even though the gonococcal fixation reaction may be positive."⁷⁵⁹ Skin tests are of uncertain value.¹⁷⁸⁷

Differential Diagnosis. No new data appeared.

TREATMENT OF GONORRHEA AND GONORRHEAL ARTHRITIS IN GENERAL

Until 1943 the treatment of choice for gonorrhea and its complications was sulfonamide therapy. In cases refractory to sulfonamides, fever therapy was combined with the use of sulfonamides. By 1943, due to the disappearance of sulfonamide-susceptible strains and the increased spread of sulfonamide-refractory strains of gonococci, the percentage of patients cured by sulfonamides had fallen from the original 70 or 95 per cent to somewhere between 30 and 75 per cent.^{350, 113, 415, 1069, 1146, 1788, 1983} In a few cases gonorrheal arthritis was cured by pro-min,⁵⁸⁰ sulfapyridine,¹⁸¹⁷ sulfathiazole¹²¹⁹ and neoprontosil.¹¹⁹

Fever therapy gave cures in 79 per cent of 1,843 collected cases of gonorrhea and its complications, but the mortality rate was 0.6 per cent (one death in every 171 cases).¹⁸⁵ In 82 to 100 per cent of cases sulfonamide-resistant gonorrhea was cured by combining fever therapy with the preliminary use of sulfonamides.¹⁶⁷⁶

PENICILLIN FOR GONORRHEA

Since 1943 penicillin has become the treatment of choice. In 95 to 98 per cent of all cases a single course of sodium penicillin, given intramuscularly or intravenously, will cure uncomplicated gonorrhea, including the sulfa-resistant type.^{162, 352, 413, 478, 829, 831, 928, 958, 1515, 1717, 1788, 1790, 1826, 1828, 1816} An adequate course comprised 20,000 units given every three hours for six doses. The few patients (2 to 5 per cent) who failed to respond to one course, practically always responded to a second. The method of Romansky (a single injection of 150,000 units of calcium penicillin in beeswax-peanut oil) was widely approved.^{1788, 1816}

PENICILLIN FOR GONORRHEAL ARTHRITIS

In the literature on penicillin under review (1943 to 1945, inclusive) we found mention of only 71 cases of gonorrheal arthritis treated with penicillin. Of these 71 cases only four were of proved gonorrheal arthritis, that is, cases in which gonococci had been recovered from synovial exudate.^{23, 831, 1107} The remaining 67 cases must be classified as presumptive gonorrheal arthritis. In most of these no articular cultures had been made; in a few, cultures of synovial fluid had been made but were negative. Practically none of the cases were reported in detail. They were merely spoken of as cases of "gonorrheal arthritis," "acute gonorrheal arthritis," "arthritis with gonorrhea," "subacute arthritis with gonorrheal urethritis" or "complicating arthritis." ^{162, 217, 413, 110, 451, 478, 531, 751, 928, 1074, 1220, 1221, 1241, 1270, 1830, 1378, 1153, 1481, 1545, 1717, 1719, 1746, 1790, 1816, 1883}

Assuming for the moment that all 71 were actually cases of gonorrheal arthritis, results of use of penicillin can be summarized briefly (table 1). Of the 68 acute cases four were of proved, 64 were of presumptive gonorrheal arthritis. Cure was attained in all of the proved cases, but in only 59 per cent of the presumptive cases. In two proved cases penicillin, given intravenously or subcutaneously was promptly effective. In the two other proved cases only partial improvement resulted from the intramuscular or intravenous administration of 160,000 units given within 48 to 60 hours, whereupon in each case penicillin was given intra-articularly once a day for three days (a total of 8,700 and 10,000 units respectively) with prompt cures.

Of the three patients with chronic presumptive gonorrheal arthritis two (no details) were not cured.¹⁰⁷¹ One patient who had presumptive gonorrheal arthritis of more than three years' duration [Difficult to believe.—Ed.] was reported as being cured promptly.¹⁷⁴⁶

TABLE I
Results from Penicillin for Gonorrheal Arthritis

Type	Total Cases	Cured		Not Cured	
		Cases	Per Cent	Cases	Per Cent
Acute:					
Proved*	4	4	100	—	—
Presumptive	64	38	59	26	41
Total acute	68	42	62	26	39
Chronic:					
Proved*	0	—	—	—	—
Presumptive	3	1	33	2	67
Acute and chronic (Proved and presumptive)	71	43	61	28	40

* Proved: gonococci cultured from synovial exudate.

Of the 68 patients with acute gonorrheal arthritis, proved or presumptive, 62 per cent were cured, 38 per cent were not. Of the total 71 cases, acute or chronic, proved or presumptive, cure was obtained in only 61 per cent. Results for those cured were described as "dramatic," "unequivocal within 48 hours," "striking," "excellent," "immediate," "complete and rapid within a few days."

Reasons for Failure of Penicillin. If penicillin cures 90 to 98 per cent of all patients who have genital gonorrhea and its nonarticular complications why does it cure only about 61 per cent of patients who have gonorrheal arthritis? Why did it fail to cure 28 of the 71 patients? Several reasons have been advanced as possible causes for these failures.

1. *Inadequate Dosage.* Some failures admittedly resulted from the use of total doses (between 60,000 and 100,000 Oxford units) now known to be sometimes inadequate. No future failures should be properly attributed to inadequate doses.

2. *Supposedly Inadequate Concentrations of Penicillin in Synovial Fluid.* Certain failures have been explained by the curious notion that penicillin, given intramuscularly or intravenously does not get into the articular cavity in sufficient concentrations to cure gonorrheal arthritis. But penicillin in doses of 25,000 to 40,000 units given intramuscularly or intravenously every three hours, does penetrate rapidly into synovial fluid and attains concentrations comparable with those in serum (Balboni, Shapiro and Kydd; Rammelkamp and Keefer). In any event gonorrheal arthritis is not a disease of the articular cavity but of synovial and periarticular tissues. Since these tissues are highly vascular, even more so when inflamed, there is no reason to suppose that penicillin entering vessels of articular tissues should not reach infected regions.

3. *Penicillin-Resistant Gonococci.* Although certain bacteria have been made resistant in vitro to penicillin,⁵⁶ development of clinical resistance has not become a problem. Such an eventuality may be prevented, in part, by the use of adequate, not minimal, doses of penicillin.

4. *Tardiness in Treatment.* This may have accounted for certain failures as several of the patients had previously been treated unsuccessfully with sulfonamides.

5. *Ineffective Penicillin.* For a few months in 1945 commercial penicillin contained inordinate amounts of the relatively ineffective penicillin K. Ineffective

penicillin cannot be blamed for future failures as commercial preparations now contain a preponderance of potent penicillin G.

6. *Errors in Diagnosis.* The most common cause of past and future "failures" from penicillin has probably been and will be error in diagnosis. Experiences at an Army Rheumatism Center revealed that most cases of so-called gonorrheal arthritis resistant to penicillin were not of gonorrheal arthritis at all but were cases of rheumatoid arthritis in men who also happened to have gonorrhea, or of rheumatoid arthritis precipitated, reactivated or aggravated by genital (not articular) gonorrhea (Hench and Boland). This was shown by negative responses to therapeutic tests with high doses of penicillin (sometimes also sulfonamides or fever therapy), by the frequent involvement of new articular sites during treatment, by the subsequent course and slow development of symmetric fusiform polyarthritis as characteristic of rheumatoid arthritis, and in some cases by articular biopsies which revealed changes characteristic of rheumatoid arthritis, unlike those usually seen in acute or subacute gonorrheal arthritis.

Thus acute genital gonorrhea is just one more acute infection which, like tonsillitis, influenza, scarlet fever and others, can act as a trigger mechanism for the production of rheumatoid arthritis. Acute gonorrhea can provoke the first appearance of rheumatoid arthritis, reactivate previously active but currently quiescent rheumatoid arthritis, or aggravate notably a coexistent rheumatoid arthritis. Thus it would appear that "post gonorrheal rheumatoid arthritis" is now more common than gonorrheal arthritis.

Recommended Dosage of Penicillin. Penicillin should be given intramuscularly in doses of 25,000 to 30,000 units every three hours for seven to 10 days. If noticeable improvement does not occur within three or four days, intra-articular injections of penicillin of at least 10,000 to 20,000 units should be made once daily in joints large enough to be so treated (Herrell).⁸³⁰ [If the intramuscular doses are large, intra-articular doses probably will be unnecessary.—Ed.]

Hypersensitivity to Penicillin Resembling Serum Sickness. No serious toxicity to sodium penicillin has been noted. The calcium salt also is nontoxic and more stable.⁸³¹ But recently reported were several cases of delayed sensitivity to penicillin, resembling serum sickness (see "Pharmaceutic Arthritis").

TUBERCULOUS ARTHRITIS

Incidence. Of 4,252 tuberculous patients 160 (3.8 per cent) had tuberculosis of bones, joints or both (Rosencrantz, Piscitelli and Bost).

Clinical Data. Physicians are tempted to regard a tuberculous joint as localized arthritis. "A tuberculous joint is always a local manifestation of a systemic disease." One should automatically search for tuberculosis elsewhere in the body.^{314, 777, 1062} Pulmonary tuberculosis was associated in 42 to 74 per cent of recent cases of bone and joint tuberculosis^{777, 1290, 1505}; and genitourinary tuberculosis in more than 20 per cent of one group.¹⁵⁰⁵

New clinical, roentgenologic and statistical studies appeared.^{777, 1057, 1093, 1290, 1505} One hundred patients, aged one to 16 years, were compared to 100 adult patients; pulmonary lesions were present in 42 per cent of the former, in 55 per cent of the adults (Nathanson and Cohen).¹²⁹⁰ More than one articular or osseous region was affected in 28 per cent of the 100 adults and 35 per cent of the children; as many as seven regions were affected in a single patient. In eight of the 160 patients of Rosencrantz,

Piscitelli and Bost¹⁵⁰⁵ one joint was considered the sole focus, no other tuberculous lesions being found.

[In statistical studies tuberculous lesions of joints are too often grouped inseparably with those of bones; hence, precise statistics on tuberculous arthritis are sometimes not obtainable.—Ed.]

Diagnosis. Diagnosis of tuberculous lesions of spine and joints should not be attempted from roentgenograms alone. Formation of bone does not always indicate secondary infection.^{134, 1290, 1380} Features supposedly "characteristic" of tuberculous arthritis may be absent. Roentgenograms in lymphatic leukemia, septic arthritis and so forth, may simulate those in tuberculous arthritis.¹⁰⁹³

Biopsy of regional lymph nodes was considered of diagnostic value.^{635, 1894} Such biopsies were positive in 15 (94 per cent) of Gellman's⁶³⁵ 16 cases of proved tuberculosis of bones or joints. The technic is simple and harmless; there are no contraindications. When conservative treatment is planned such biopsy is preferable to articular biopsy. It often can be done when a patient is "afraid to have a joint opened." But Webster warned against incautious interpretations of such biopsy material. Tuberculous inguinal adenitis was found in six of seven cases of tuberculous knees, in two of six cases of probable tuberculous hips, and in an adult with a tuberculous ankle. But in two cases of tuberculosis of the hips the inguinal adenitis appeared to have resulted from cutaneous tuberculosis rather than from tuberculous hips. A positive finding was of value; a negative biopsy was merely "inconclusive." [We prefer articular biopsies.—Ed.]

Special Localization: Clinical Data and Treatment. Tuberculosis affects chiefly weight-bearing joints, especially spine and hips.¹⁵⁰⁵

1. *Spine.* This was affected in 41 per cent of one series¹⁰⁵⁷; in 33 per cent of another.¹⁵⁰⁵ The upper thoracic vertebrae are more often affected in children; the lower thoracic in adults. Vertebrae may be attacked primarily in the anterior, central or posterior portions as well as at margins. Marginal involvement occurs most often in adults.¹²⁹⁰ In Pott's disease caseation of bone and soft tissue occurs first, then bony sclerosis. The latter is a vascular phenomenon resulting from loss of blood supply from thrombosis or endarteritis, or from occlusion or destruction of blood vessels by dissecting abscesses, according to Cleveland and Bosworth. In cases of tuberculous spondylitis, paravertebral abscesses may rupture into pleura or lung,²¹⁸ into mediastinum¹⁶⁶⁸ or into dura causing the Brown-Séquard syndrome.⁷⁵

New roentgenographic studies stressed the following: Roentgenograms often fail to reveal spinal tuberculosis; they never reveal the full damage.³²⁶ Bridging of vertebrae in spinal tuberculosis, formerly considered indicative of secondary pyogenic infection, probably is a reaction to irritation with periosteal formation of new bone or ligamentous ossification; it is not a healing process.¹³⁸⁰ Serial roentgenograms reveal first a thin disk (of early diagnostic importance), then a thinner disk with adjacent vertebral caries; finally disappearance of the disk, advanced caries and collapse of vertebral bodies.⁷⁷⁶ Spinal pain intensified by movement, weight-bearing and jolting, relieved by rest, early evidence of thinned disk and isolation of tubercle bacilli from aspirated pus are points in early diagnosis.

Principles and results of treatment were discussed.^{11, 13, 191, 313, 1006, 1062} Comparing three different technics in the surgical treatment in 123 cases, Bosworth and Haines found no advantage in using extra bone from tibia. Child preferred conservative, nonsurgical treatment in juvenile spondylitis.

2. *Hips.* Differentiation in children is simplified if one remembers that the common age of onset of tuberculosis of hips is one to five years, of Perthes' disease

between five and 10 years and of slipped femoral epiphysis between 10 and 15 years of age (Cholmeley). The roentgenographic localization of cavities and tuberculous foci in hips was discussed.¹⁹⁶³ In early tuberculosis of hips and in septic arthritis of hips but not in other conditions, the intrapelvic shadow cast in roentgenograms by the obturator internus muscle becomes obscured or widened; such a "positive obturator sign" is of diagnostic importance.⁸⁰⁸

Results from arthrodesis were reported.^{314, 370} Roth¹⁵¹⁰ considered fusion contraindicated in children less than six years old and "relatively contraindicated" in those between six and nine years old.

3. *Greater Trochanter and Bursa.* Trochanteric bursitis is often secondary to tuberculosis of the greater trochanter.⁴⁷⁷

4. *Sacroiliacs.* For early diagnosis the "Nachlas knee flexion test" was recommended.¹⁰⁰⁶

5. *Knee.* Tuberculosis of knees may long, sometimes permanently, remain confined to synovia and not invade adjacent bone. In such cases roentgenograms are valueless for early diagnosis.¹³⁴² If involvement of bone can be avoided, full motion may be obtained in 30 per cent of cases.¹⁰⁶² In cases of chronic monarticular synovitis with synovial thickening and periarticular infiltration but no effusion, suspect "potential tuberculous infection" until the contrary is proved (Langston).¹⁰⁶²

[This old axiom used to be statistically correct and useful, but tuberculosis of joints is now so (relatively) rare that a case of chronic monarthritis nowadays is much more likely to represent atypical monarticular rheumatoid arthritis than tuberculous monarthritis.—Ed.]

Extra-articular arthrodesis gave results satisfactory to King and Richards¹⁰⁰¹ but is not applicable to children as it may arrest growth. Nonsurgical immobilization was recommended for children.¹⁰⁶²

6. *Other Joints.* Shoulders are affected in less than 1 per cent of cases of bone and joint tuberculosis.¹⁰⁶² Extra-articular fusion of tuberculous shoulders was successful after conservative or intra-articular fusion failed (Murphy and Wood).¹²⁷⁷

General Remarks on Treatment and Prognosis. Attempts to treat the local lesion and ignore the general infection are doomed to partial or total failure. The proper employment of rest is the greatest single therapeutic factor. Once a joint is infected, recurrence of disease is likely unless treatment has restored full motion or provided firm ankylosis.^{370, 777, 1057, 1062} In general surgical treatment is superior to nonsurgical. Of 118 patients treated conservatively (rest, immobilization) 16 per cent became well; 16 per cent improved; 14 per cent were unimproved; and 54 per cent died. Of 85 patients treated surgically 19 per cent became well; 27 per cent improved; 9 per cent were unimproved; and 45 per cent died (Rosencrantz, Piscitelli and Bost¹⁵⁰⁵).

[The use of streptomycin may improve this gloomy picture. Preliminary results are encouraging.⁸⁵⁰ Early tuberculous lesions confined to synovia may heal. As currently used, streptomycin will not replace operations for advanced destructive lesions.—Ed.]

"TUBERCULOUS RHEUMATISM" (PONCET'S DISEASE) AND NONDESTRUCTIVE TUBERCULOUS POLYARTHRITIS

The concept that tuberculosis can produce not only the characteristic, accepted type of tuberculous arthritis (a destructive monarthritis or oligoarthritis with invasion by tubercle bacilli and tubercles) but also an acute polyarthritis resembling rheumatic fever or a chronic nondestructive polyarthritis resembling rheumatoid arthritis was introduced by Grocco (1892), publicized by Poncet (1902),

and more recently endorsed vigorously by Reitter and Loewenstein (1933) and others.^{10, 1d} This "tuberculous rheumatism" presumably results from the invasion of joints by tuberculous toxins from distant foci; hence, tubercles and tubercle bacilli are not found in affected articular tissues. This concept has found practically no support in the United States (Brav and Hench, 1934^{1b}).

In 1938 Reitter and Loewenstein claimed to have recovered tubercle bacilli from the blood in a variety of conditions including different types of acute and chronic arthritis. This work found few supporters.¹¹¹⁹ Loewenstein again claimed to have found tubercle bacilli in blood and synovial fluid of patients during life and from blood, heart, spleen and tonsils at necropsy in cases of rheumatic fever, endocarditis and chorea. In certain cases of untreated rheumatic fever miliary tuberculosis has developed. Sensitivity to tuberculin changes from anergy in early rheumatic fever to hyperergy during convalescence. According to Loewenstein¹¹¹⁹ recurrent attacks of rheumatic fever result from endogenous or exogenous reinfection; superimposed infections may mobilize "sleeping foci" of tubercle bacilli; the clinical and anatomic features may be allergic.

Two critical observers, denying much of Poncet's theory and unable to accept the claims of Loewenstein have, nevertheless, presented two cases in partial support of the original thesis.

Montuschi presented the following case: Bilateral pleural effusion developed in a young man and lasted for several months; then acute febrile polyarthritis occurred; it disappeared after three weeks. The tuberculin test was strongly positive although tubercle bacilli were never found in sputum and roentgenograms of chest revealed indefinite findings. For reasons stated a presumptive diagnosis of tuberculous rheumatism was made.

A case with more definite findings was reported by Kling and Levine as one of nondestructive tuberculous polyarthritis (not "tuberculous rheumatism"). As a child, the patient had lived with tuberculous relatives. At the age of 25 years she had active pulmonary tuberculosis. At age 28 years when the roentgenogram revealed *no* active pulmonary disease, chronic arthritis of a knee and subacute recurrent arthritis and arthralgia in several other joints developed. The condition was called "rheumatoid arthritis" in the United States, "benign tuberculous rheumatism, Poncet type" when she went to Europe. At age 35 years fluid aspirated from a knee was negative on guinea pig test. Synovectomy was done; objectively the articular inflammation resembled a nonspecific, nondestructive synovitis but, surprisingly, synovia contained miliary tubercles; a few bacilli were found by staining; a guinea pig inoculated with macerated synovia developed glandular and visceral tuberculosis in six weeks. Kling and Levine concluded: Mild tuberculous nondestructive polyarthritis does occur as a hematogenous infection of joints from a visceral focus in a person with high tissue resistance. No diffusible tuberculous toxins have been identified. "It is not proved that the tubercle bacillus or its products are able to produce other than specific pathologic changes."

[An interesting, thought-provoking case which indicates that tuberculous arthritis may be polyarticular and of relatively nonspecific *clinical* type. But this case is one of tuberculous polyarthritis and does *not* support the concept of "tuberculous rheumatism."—Ed.]

OSTEITIS TUBERCULOSA MULTIPLEX CYSTOIDES

This represents sarcoidosis of bone and will be discussed under "Miscellaneous Conditions: Sarcoidosis."

PNEUMOCOCCAL ARTHRITIS

The incidence of arthritis as a complication of pneumonia is about 0.3 per cent. Primary or "cryptogenic" pneumococcal arthritis may occur without pneumonia (Blankenhorn and Grupen; Bogers¹⁶⁶). There is no evidence that specific arthrotropic pneumococci exist. Although any joint may be involved, usually only one or two large ones are affected. Clinical features are like those of other acute specific pyogenic arthritides. Therapy with type specific *Pneumococcus* serum was successful¹⁵⁴ but sulfonamides are the drug of choice. Supplementary intra-articular instillation of sulfathiazole or sulfadiazine was considered of value.^{166, 353} Penicillin should be equally efficacious. Combined with specific therapy, repeated joint aspirations were preferred to arthrotomy.^{154, 166} Prognosis in the primary type of arthritis, formerly considered grave, appears to be excellent but prognosis in the secondary type depends on the severity of the focus of infection or bacteremia. Slight, if any, residual articular damage is to be expected if prompt and adequate therapy is instituted. An unusual case was reported in which spontaneous recurrence of suppuration occurred months after apparent healing.³⁵³

SYPHILITIC ARTHRITIS AND SYNOVITIS

Articular disorders due to congenital or acquired syphilis were tabulated and discussed (Comroe³⁶³; Steindler). Of 2,400 syphilitic patients 119 (5 per cent) had skeletal lesions and 63 of these 119 had articular lesions: 22 had synovitis (nine associated with congenital, 13 with acquired, syphilis), 43 had Charcot's joints and five prepatellar bursitis from acquired syphilis.^{237, 238} Wassermann tests on synovial fluid were positive in six of the nine cases of congenital syphilis and synovitis, in 10 of 11 tested cases of synovitis and acquired syphilis, in five of seven tested cases of tabetic joints.

In early congenital syphilis articular lesions are rare and leave no residual enlargement. In late congenital syphilis nongummatous articular lesions usually involve large joints and under treatment symptoms disappear. But gummatous articular lesions may produce synovitis, pannus, destruction of cartilage and residual damage.¹⁷¹⁰ Syphilitic spondylitis with invasion of bone and periosteum by *Treponema pallidum* has a predilection for the cervical region; it is not to be confused with Charcot's spine. Six cases were reported, one of which was verified at necropsy (Freedman and Meachan⁵⁹⁴; Sgalitzer). On clinical and roentgenologic grounds syphilitic spondylitis can be distinguished from tuberculous, rheumatoid or osteoarthritic spondylitis. Syphilis of a biceps tendon and olecranon bursa with *Treponema pallidum* in granulation tissue was noted (Schrager¹⁵⁵⁶). Juxta-articular nodules (subcutaneous fibroid syphilomas), rare lesions of late syphilis, have a predilection for elbows and knees and must be differentiated from the nodules of rheumatoid arthritis, gout, tuberculosis, xanthoma and various tumors.^{941, 1304, 1827}

[The reported incidence of syphilitic arthritis or synovitis is falling notably as more exact diagnostic criteria are used. Many articular lesions, once considered syphilitic, are no longer so regarded. In our experience articular lesions of syphilis are much rarer than even current literature suggests. We agree with others²³⁸ that the mere presence of an articular lesion or a positive Wassermann reaction of synovial fluid of a syphilitic does not necessarily indicate that the joint is syphilitic; most of them are not. The best diagnostic test aside from articular biopsy is a rapid response to antisymphilitic therapy; even this is not infallible.—Ed.]

TABETIC AND NONTABETIC NEUROARTHROPATHIES: CHARCOT'S JOINTS

Typical Charcot's joints occur not only in tabes dorsalis but also in certain neurologic conditions: syringomyelia; tumors and injuries of spinal cord; spina bifida with involvement of nerves; neuritis or injury of peripheral nerves; leprosy and so forth.^{204, 1374, 1400, 1711, 1817, 1956}

Tabetic Arthropathy. Charcot's joints develop in 5 to 10 per cent of cases of tabes.^{1400, 1711} Often the joint symptoms first call attention to the underlying disease of the nervous system. Spinal fluid and serologic tests on blood for syphilis may give negative results in 50 per cent, but history and neurologic findings confirm the diagnosis. Usually one major weight-bearing joint is affected, but multiple joints may be involved.¹⁷¹¹

In a study of 58 cases by Pomeranz and Rothberg joints affected were (in percentages): knee 38; tarsal 19; hip 18; ankle 8; spine 6; toes 4; shoulder 4; pelvis 3. More than one joint was affected in 32 per cent and symmetrical joints in 20 per cent. Clinical and statistical analyses of 214 Charcot's joints in 134 patients were made by Steindler, Williams and Puig-Guri. Cases of involvement of hip,¹⁹⁶⁰ knee¹⁰⁶⁶ and metatarsophalangeal joints of big toes¹³³³ were reported: in one case serial roentgenograms showed the progression in a hip in one year.¹⁰⁶⁰ Charcot's joint presents "an exaggerated form of osteoarthritis" (King¹⁰⁰²); differentiation of tabetic hip from osteoarthritic hip was discussed.⁹⁷¹

The pathogenesis of this articular disease is incompletely understood. Charcot stated that the changes were trophic in origin as a result of disease of the anterior horn cells or degeneration of peripheral nerves. But currently accepted¹⁷¹¹ was the concept of Eloesser (1917) who found that bone and joint changes corresponding to those in Charcot's joints could only be produced in animals by cutting the posterior nerve roots and then subjecting joints to trauma; in the absence of trauma, no arthritis developed. This agrees with observations in man that acute trauma frequently (40 per cent of cases) precedes the development of a Charcot joint.¹⁷¹¹ Pain may be a manifestation of a Charcot joint. It occurred to some degree in 56 of the 58 cases of Pomeranz and Rothberg.

Syringomyelic Arthropathy. In about 25 per cent of cases of syringomyelia Charcot's joints, arthropathies locally indistinguishable from tabetic joints, develop. But tabes affects upper extremities much less frequently than does syringomyelia.^{1400, 1711} A case of syringomyelia was studied with serial roentgenograms: extensive destructive changes developed in a shoulder within seven weeks (Pendergrass, Gammon and Powell).

"Charcot Joints" (Unclassified). The synovial membrane in a Charcot joint (unclassified as to type, whether tabetic or otherwise) revealed retrogressive alterations (atrophy, degeneration, necrosis) but also progressive and proliferative changes and well-developed Golgi networks (King).¹⁰⁰² Radiographically the following sequence of events occurred in Charcot's joints: hydrarthrosis, disintegration, hypertrophy, atrophy; these stages were illustrated.^{204, 1817}

Treatment of Charcot's Joints. Current reports concerned tabetic joints chiefly. Treatment is unsatisfactory. Tabetic joints are not affected by anti-syphilitic therapy. Conservative orthopedic treatment (nonsurgical immobilization) was recommended by some who considered attempts at surgical fusion often disappointing.^{1400, 1711, 1956} Others favored surgical fusion.⁹⁹⁷ A tabetic knee was thus successfully treated (Lapidus).¹⁰⁶⁶

YAWS (*FRAMBESIA TROPICA*)

Yaws is a specific endemic tropical disease caused by the spirochete, *Treponema pertenue*, morphologically indistinguishable from *Treponema pallidum*. Because of this and because the manifestations of yaws are so like those of syphilis, some writers consider the two conditions identical. Others emphasize the distinctions: yaws is not a venereal disease; it rarely attacks viscera or central nervous system; but like syphilis it attacks bones and joints, the acute lesions of which were discussed by Helfet. Acute juxta-articular osseous lesions may simulate acute arthritis with pain, tenderness, swelling, spasm and limited motion. Joints and tendon sheaths may be chronically affected: a relatively painless progressive proliferative synovitis occurs, apparently without involvement of cartilage. A photomicrograph of affected synovial membrane was shown. Spinal involvement often results in ligamentous calcification, localized or diffuse, resembling ankylosing (rheumatoid) spondylitis. Tendinous ganglia often appear. Wassermann and Kahn reactions are invariably positive. Treatment with arsenicals reduces most symptoms rapidly; swelling slowly.

BRUCELLOSIS: UNDULANT (MALTA) FEVER

Incidence. Between 1930 and 1943, 36,513 cases were reported from the United States.⁸⁹⁷ Some authors feared that the increasing prevalence and failure of recognition might present a serious problem.^{296, 563, 772, 783, 1826} Others were less perturbed: exposure is fairly common, but the disease is subclinical and harmless in most cases (Goodman).⁶⁷⁸

Brucellosis is more common in rural communities but is common in all groups, particularly among laboratory workers, farmers, butchers, slaughterhouse employees and veterinarians.^{772, 783} The method of transmission may be materially different in various areas. Cases from direct contact are more frequent than those from contaminated dairy products.

That children are less susceptible than adults^{291, 1684} was doubted by Hagebusch and Frei who in three years saw 182 children with brucellosis; 95 per cent of them were less than six years of age. Maternal infection can be transmitted to the child in utero or during delivery.

Clinical Data. Brucellosis in the general population may be acute, chronic or latent and asymptomatic. The goat strain of *Brucella* produces the most violent effect in man, the porcine less severe and the bovine least severe.⁸⁵⁴ The manifold clinical manifestations were reviewed.^{446, 705, 783, 1150, 1684, 1685} Acute brucellosis is a clear-cut clinical entity¹⁸³⁵ but probably less than 10 per cent of patients with chronic brucellosis give a history of a previous acute attack.^{854, 1088} Splenomegaly was the most consistent finding in acute infections; it was noted in 34 per cent of cases (Levitt).

Chronic brucellosis is difficult to recognize. Fever is not always present; it was absent in 23 per cent of cases (Griggs)⁷⁰⁵; when present, it seldom runs a wavelike course (Holbrook).⁸⁵⁴ Suggestive features are fatigability, weakness, lethargy, headache, abdominal pain, constipation, colitis, pelvic disorders, menorrhagia,⁴⁴⁶ nervousness and insomnia. In many cases a diagnosis of neurasthenia is made. Ocular, oral, pulmonary, cardiac and lymphatic manifestations were described with splenomegaly in 40 per cent of cases (Spink and Hall). The spleen may be greatly enlarged¹⁰⁶⁷; sterility has occurred.⁷²⁹

Symptoms Referable to Muscles and Joints. Arthralgia and general aches in muscles, limbs and joints also were described.^{705, 1058, 1150, 1610, 1684, 1685} In five

of 100 cases of chronic brucellosis destructive bone lesions were present (Griggs).⁷⁰⁵ In one series of 48 cases "arthritic pains," including backache were found in only 8 per cent (Urschel).¹⁸³⁶ Periarthritis, bursitis and hydrarthrosis may be observed (Carpenter). Spondylitis probably is the most common articular or osseous complication of brucellosis¹³⁸⁶; 68 cases of brucellar spondylitis, usually lumbosacral, have been recorded in the literature. (Spink and Hall). Localization to the spinal region has occurred from three weeks to one year after the original infection.¹³⁸⁶ Five cases of destruction of lumbar vertebrae were reported.^{472, 835, 1386, 1684}

Pain and stiffness of spine were usual symptoms. The lumbar and thoracic regions were most often affected. The picture was generally more acute but more benign than in tuberculosis. Formation of abscesses and deformity were rare as destructive changes were not extensive. Roentgenograms characteristically showed a zone of sclerosis spreading to involve the whole vertebrae. The disk was involved late.

As cases of brucellar spondylitis unlike the destructive cases just described Goldfain⁶⁶⁴ reported five cases resembling rheumatoid (ankylosing) spondylitis, Marie-Strümpell type. Diagnosis was based on positive agglutination and skin tests and opsonic indexes.

[The case reports were meager. Roentgenographic changes were not described. It is probable that these patients had rheumatoid spondylitis and unrelated coincidental brucellosis.—Ed.]

Brucellosis must be considered in the differential diagnosis of all types of arthritis; when raw milk is used, a high percentage of "run-of-the-mill" cases of arthritis are associated with *Brucella* infection and respond to specific therapy, according to Harris. [We do not agree.—Ed.] The arthritis is likely to be atypical and joint involvement bizarre. Acute joint manifestations may resemble those of rheumatic fever.^{772, 1819} Chronic brucellosis was considered by Goldfain^{662, 664} to be the cause in two typical cases of rheumatoid arthritis.

Such reports prompted Green and Freyberg⁶⁹⁵ to study the incidence of active brucellosis in patients with rheumatoid arthritis and other rheumatic disease. No brucellosis was found in 25 cases of typical rheumatoid arthritis. Of 25 patients with miscellaneous rheumatic disorders, three had active brucellosis, six had possible brucellosis. Green and Freyberg⁶⁹⁵ concluded: "Arthralgia and other rheumatic symptoms are common in brucellosis, and *temporary* non-purulent joint inflammation may occur, but brucellosis is seldom if ever the cause of *chronic* non-purulent joint inflammation."

[Many physicians in the Southwest have been led to "think first of brucellosis" in almost any case of chronic arthritis. But in our experience brucellosis is about the last thing to think of as the cause of chronic arthritis of the rheumatoid type.—Ed.]

Diagnosis. A long, searching history is the first requisite.⁷⁰⁵ The diagnosis of brucellosis is established with certainty only by culture and identification of the organism from blood or tissue fluids^{773, 1088, 1619, 1835, 1952} but, unfortunately, cultures are usually negative.^{729, 772}

The inadequacy of the agglutination test was stressed by many,^{705, 729, 772, 879, 1088, 1619} but Green and Freyberg⁶⁹⁵ found it the most reliable of the common diagnostic procedures; others considered it the most sensitive test.²⁹⁶ Conflicting reports

on the value of the skin test also appeared. Some believed it to be valuable^{705, 772, 783}; others disagreed.^{678, 1610} A positive test indicates only that the patient has been sensitized some time.²⁹¹ Urschel¹⁸³⁸ considered brucellergin the best antigen for routine skin tests.

[Intradermal skin tests may be very irritating; unless control tests are made an "irritation reaction" may be misinterpreted as a positive reaction. Skin tests made in active cases of brucellosis are not without danger; there is a 30 per cent chance of producing an Arthus phenomenon which may result in ulcer formation lasting weeks or months.—Ed.]

Most writers were skeptical of the value of the opsonocytophagic test,^{291, 678, 695, 1684} but Harris⁷⁷² found it accurate in diagnosis and helpful in prognosis. The various tests must be correlated with the clinical picture. Animal inoculations may be of value.^{291, 783} A provocative test with typhoid vaccine should constitute one of the diagnostic methods.⁷⁸³ Sedimentation rates are increased in a small proportion of cases. Leukocyte counts may be low, normal or high.⁷⁰⁵ The important factor is the presence of a relative or absolute lymphocytosis.¹⁶⁸⁴ Eosinophilia was noted.⁶²⁵ The diagnosis of *Brucella* infection often has to be made by exclusion.¹⁸³⁵ [But many presumptive diagnoses of brucellosis are, in our opinion, inaccurate.—Ed.]

Treatment. No one method of treatment can be relied on in all cases.⁷⁷² Evaluation of remedies is difficult as most patients with early disease respond to rest in bed and symptomatic treatment. "Successful results" should often be attributed to the nature of the disease rather than to the agent used.⁸⁷⁹

1. *Chemotherapy.* After reviewing the literature on sulfonamides Urschel¹⁸³⁷ concluded that their use is not warranted in brucellosis.^{95, 446, 854, 870, 1097} Many agreed, but others approved their use in acute cases.^{729, 772, 1681} They are valuable only if they produce a severe drug reaction.⁷⁸³ Treatment with sulfaguanidine and sulfasuxidine was satisfactory (Davis⁴⁴⁷; Sarvis). Strains of *Brucella* are resistant to penicillin in vitro (Spink). Penicillin was not effective in experimental brucellosis of guinea pigs.¹⁷⁴¹

2. *Serums and Vaccines.* Heat-killed *Brucella* vaccine was considered effective by some.^{700, 772, 843, 1088} Equally good results were obtained with brucellin.^{783, 1619} Brucellin was used in more than 3,000 cases but was not always successful according to Huddleson. Convalescent human blood or serum was considered useful in acute cases by some (Carpenter; Hartsock), but remissions may occur.⁸⁷⁹ Foshay's serum was reported to have been "100 per cent effective" in acute cases of one to four months' duration.⁷²⁹

3. *Fever Therapy.* This was considered best in cases in which the disease was refractory to vaccine, and was thought to be useful in cases of localized infection or in cases of acute or subacute *Brucella* arthritis.^{772, 773} It was reported as being effective in most cases of brucellosis, including three cases of *Brucella* spondylitis.¹³⁵⁶ It supposedly produced remission in 13 of 18 cases of brucellosis.^{932, 933}

4. *Other Treatment.* Typhoid vaccine⁷⁷² given intravenously was of no value. In a preliminary note, Schreiner reported that five patients were treated successfully with radioactive colloidal manganese. A successful method of treatment still awaits development.⁶⁷⁸ [There is as yet no specific treatment for brucellosis.—Ed.]

5. *Prophylaxis.* Protection may be afforded to humans by vaccine, but further studies are essential.^{291, 1025, 1026, 1027, 1619, 1020}

TYPHOID ARTHRITIS

Monarticular, less commonly a polyarticular, arthritis is an occasional complication of typhoid fever. "Typhoid spine," an inflammatory lesion of vertebral

periosteum, is usually of low grade and tends to be chronic. Abscess formation rarely occurs. Lower thoracic and lumbar vertebrae are affected most commonly. Tenderness, muscle spasm, limited motion, scoliosis and kyphosis may occur. Usually only two contiguous vertebrae are affected. The intervertebral disk may be narrowed or absent; there is irregular density of the adjacent vertebral bodies. Perispinal ligamentous ossification is frequent and may lead to complete bony bridging of the two affected vertebrae. The diagnosis may be suspected from a history of backache during or after typhoid fever, either immediately or weeks later, and confirmed from the roentgenogram. The incidence of typhoid spondylitis is low; among a recent group of 410 typhoid patients only one had persistent backache considered to be from "typhoid spine" (McMaster). In an unusual case of typhoid spine, in which symptoms first appeared 12 years after, and suppuration 22 years after, typhoid fever, the abscess ruptured into a lung and a psoas abscess also formed (Johnson and James). Treatment of typhoid spine includes rest and immobilization with cast or back brace. In the absence of suppuration, complete recovery with good function is the rule. In severe cases spinal fusion may be indicated.^{915, 1208}

MENINGOCOCCIC ARTHRITIS

"Since the identification of the meningococcus by Weichselbaum (1887) the clinical concept of meningococcal infection has been dominated by its most serious manifestation, meningitis,"⁴⁶⁷ but "from the practical standpoint it is vital to view the disease primarily as a septicæmia, the organism invading the blood stream from nasopharynx with localization in skin, joints, meninges, and other body tissues."⁴³¹ That meningococcemia without meningitis can no longer be considered a medical rarity is supported by new studies.^{375, 431, 467, 846, 1153, 1639, 1738} In such cases a variety of diagnoses, chiefly rheumatic fever, influenza, arthritis and erythema nodosum, were reported on admission. Meningitis was not epidemic in the regions concerned.^{375, 467}

Incidence of Articular Manifestations. The loose use of the term "arthritis" by many authors made calculation of the incidence difficult (Boger).¹⁶⁷ Arthritis was the most frequent disabling complication in one series of 100 patients: 11 had definite joint symptoms (arthralgia in four, suppurative arthritis in seven).¹⁷³⁸ Of 3,005 cases of cerebrospinal fever, arthritis was a complication in 2.7 per cent (Beeson and Westerman). Among 1,000 children with meningococcic infection reported from Chile, arthritis was diagnosed clinically in 3.7 per cent, but in 13 of 52 cases in which postmortem examination was performed, purulent synovitis which had not been diagnosed clinically was discovered (Bass and Nothman). Fox and Gilbert found the incidence of articular complications to have been 1.9 per cent before the use of sulfonamides and 11.8 per cent after the advent of chemotherapy, a discrepancy which "may well be accounted for by the lessened mortality with more opportunity for complications." Meningococcic arthritis was said to occur most often in children less than two years of age (Chont).

Clinical Data. The differentiation of two types of meningococcic arthritis by Herrick and Parkhurst in 1919 (type A, early transitory hemorrhagic polyarthritis; type B, a subsequent or independently occurring monoarticular suppurative arthritis) was discussed.^{167, 297, 582, 1738} A somewhat similar distinction was made by Bauer, Ropes and Short: one type of arthritis, usually symmetrical,

may occur early in the course of the disease with little swelling or effusion but with polyarticular pain and tenderness; another type with metastatic pyarthrosis generally occurs toward the end of the last week of disease and usually affects only one joint, commonly a knee.

What is generally referred to as "arthritis" is, in most cases, an acute synovitis which usually subsides promptly with complete restoration of joint function. In exceptional cases the synovitis leads to purulent arthritis with effusion (Boger).¹⁶⁷ Purulent arthritis was noted most frequently in knees but metacarpophalangeal joints, elbows, wrists, hips and ankles also were involved.^{167, 297, 582, 954, 1153, 1738} In one patient, seven weeks of age, suppurative arthritis occurred in both hips during the second week of illness (Bass and Nothman).

Joint symptoms are not related to the objective severity of the articular disease.⁵⁵² Striking differences may occur: in one case the violence of the polyarthritides, with excruciating pain and swelling in many joints was outstanding; in a contrasting case of slight swelling in one knee, there was no pain on manipulation, no redness or tenderness although culture of synovial fluid revealed meningococci.¹⁶⁷ In another case²⁹⁷ gentle passive motion of fingers or forearm elicited screaming, but there was no articular swelling, redness or heat. Swelling, crepitation, stiffness and pain on motion may persist after other signs of infection have disappeared.¹⁷³⁸

Diagnosis may be confused by the coincidental presence of a positive gonococcic complement fixation test.^{167, 954} Spectacular improvement in joint symptoms and fever on cessation of drug therapy led to a diagnosis of sulfadiazine arthritis in two of 134 patients given massive dosage (see "Pharmaceutic Arthritis").¹¹⁵³

Pathology and Laboratory Data. No noteworthy data on the pathologic changes in meningococcic arthritis have been added to those of Keefer, Parker and Myers.^{1b} Meningococci were found in joint fluid in a third of the suppurative cases. The fluid was mucinous, serous, seropurulent or frankly purulent (Fox and Gilbert). Despite the presence of greenish or yellow purulent synovial fluid, cultures and smears of fluid were negative for meningococci in some,^{297, 1738} positive in others.^{82, 167} Cattell reported that in synovial fluid, leukocyte counts varied between 26,200 and 78,700 per 100 c.c. with 98 to 100 per cent polymorphonuclear leukocytes. Recovery of the organism from blood in nonfulminating cases was largely a matter of chance. Twenty-one samples of blood from one patient yielded only two positive cultures.¹⁶⁷ Mester's "specific" reaction was of no value in diagnosis (Copeman and Stewart). Roentgenograms made in one case after purulent arthritis had subsided were negative⁵⁸²; in others destruction, extensive demineralization and narrowing of joint space were noted.^{167, 1738}

Treatment. Chemotherapy is the treatment of choice. But the occurrence or continuance of suppurative arthritis or both sometimes were noted even when concentrations of sulfonamide in the blood should have been adequate.^{167, 297, 582, 1153, 1738} Possible reasons for such failures were given.^{297, 582, 1738}

Massive doses of sulfadiazine were recommended by Marangoni and D'Agati who considered a concentration of 15 to 20 mg. per 100 c.c. of blood optimal, but the incidence of toxic manifestations was high (28 per cent). Initial intravenous therapy was advised in seven cases of fulminating disease. Among 112 soldiers with meningococcic infections those treated with small doses of sulfadiazine fared better than those given large doses.¹³¹ A high degree of success, with a low complication rate, was attained by maintaining the concentration of sulfadiazine at 8 mg. per 100 c.c. of blood.

Strong and Hollander advocated intensive chemotherapy during the acute

stage of arthritis, aspiration of demonstrable effusion, immobilization of affected joints, and subsequent physiotherapy. According to Boger¹⁶⁷ purulent meningococcic arthritis should be treated conservatively: "The effusion frequently resolves spontaneously but large ones may call for repeated aspiration; arthrotomy seems to have no place; appropriate splinting may give great comfort." Two patients who did not respond rapidly to sulfadiazine were given polyvalent anti-meningococcic serum intravenously and recovered.⁴³¹ Three patients with meningococcemia recovered without therapy.¹⁶¹⁸ Factors other than therapy, such as the development of bactericidal powers in the patient's blood, are responsible for recovery from meningococcic infection.

Penicillin cured acute meningococcic arthritis in one case.¹³⁷⁵ [Opinions differ as to the drug of choice: some still favor sulfonamides; others believe that penicillin is generally preferable except in overwhelming infections in which case both penicillin and sulfonamides should be used.—Ed.]

Results and Prognosis. During World War I, complications and sequelae from meningococcic infections were relatively common; the mortality rate ranged from 30 to 50 per cent (Strong and Hollander). In contrast, recent reports revealed only two deaths in 100 cases,¹⁷³⁸ one in 112 cases,⁴³¹ four in 129 cases,¹¹⁵³ nine in 51 cases.¹⁶³⁹

"The prognosis of the acute synovitis is uniformly excellent but when the joint space is invaded the prognosis should be a little more guarded" according to Boger¹⁶⁷ whose review of 66 reported cases (not all proved) indicated that in 12 per cent permanent articular damage developed. In another group, more than half the patients with arthritis recovered completely (Beeson and Westerman).

SUPPURATIVE ARTHRITIS

General Comment. Suppurative arthritis may result from neighboring bone disease, penetrating injury or metastatic infection. Multiple joints may be involved.^{150, 574, 803} Persons less than 30 years of age are most often afflicted especially in hips and knees.^{150, 803} The articular picture may be masked by the systemic reaction to suppuration.¹⁵⁰

Of Streptococcic Origin. Streptococci were recovered from 45 of 150 joints cultured (Heberling). Goodyear reported polyarthritis due to *Streptococcus viridans* in an infant seven weeks old, supposedly secondary to dental focal infection in the mother. When streptococci are the causative bacteria, primary synovial infections usually result (Russo).

Of Staphylococcic Origin. Staphylococci were isolated in most cases of suppurative arthritis, since these bacteria are commonly responsible for osteomyelitis, the most frequent precursor of suppurative arthritis.⁸⁰³

Treatment. The necessity for early diagnosis (by joint aspiration and culture) and early treatment was stressed.⁵⁷⁴ Initial sedation, establishment of fluid balance, immobilization and transfusions if indicated were advised. Arthrotomy continued to have its advocates^{150, 325, 803}; a new operation for adequate drainage of the hip was described (Girdlestone). Suppuration was controlled by multiple aspirations combined with systemic sulfonamide therapy (Beach; Blaisdell and Harmon). Penicillin promptly cured septic arthritis due to *Staphylococcus aureus* in one case.⁹⁵⁸ Key⁹⁹⁶ recommended daily intramuscular and intra-articular injections of penicillin supplemented by arthrotomy if destruction of

cartilage has occurred. [Early judicious use of chemotherapy, antibiotics and frequent aspirations of joints may prevent many arthrotomies in the future.—Ed.] Immobilization of joints by traction or plaster and also the early use of active motion were generally advised (Heberling). [With fewer arthrotomies necessary, perhaps active motion can be instituted earlier while joints are still in traction, with the hope of obtaining better functional results.—Ed.]

The later treatment is instituted the less satisfactory are end results, because of excessive damage of cartilage resulting from improper drainage related to formation of pockets by adhesions.⁸⁰³ Results were generally poor in some series of cases.^{325, 1518} After study of 147 suppurating hips in 132 patients, Harmon and Adams⁷⁶⁷ concluded that the course was benign in patients less than three years of age, in those with minimal or no bone involvement, and in those who had early arthrotomy with prolonged continuous extension. Positional correction of a single ankylosed hip, subsequent ankylosis of a painful hip, and certain plastic operations in juveniles were more satisfactory to Harmon and Adams⁷⁶⁸ than arthroplastic procedures. A reconstruction operation for dislocation of hips secondary to suppurative arthritis utilized potential growth of the upper part of the femur in the very young (Harmon).⁷⁶² An arthroplasty for ankylosed knees and elbows in which the joint was reshaped into a simple ginglymus was described (Hass).⁷⁹³

PENICILLIN AND SULFONAMIDES IN THE TREATMENT OF BACTERIAL ARTHRITIS EXCLUSIVE OF GONORRHEA

The effectiveness of sulfonamides against infectious arthritis due to pyogenic streptococci and *Escherichia coli*, was confirmed in one report (Bauer, Ropes and Short⁹⁵). But the impression of its authors that staphylococcic and meningococcic arthritis could be effectively treated by sulfonamides was not upheld by others (Frankel and Larkum; Fox and Gilbert⁵⁸²).

That penicillin is even more efficient against infectious arthritis than sulfonamides was indicated by many.^{162, 451, 829, 831} Following intramuscular administration penicillin is present in adequate amounts in the synovial fluid.^{63, 1182} By intra-articular injection of 25,000 units of penicillin a therapeutic level was maintained for two days thereafter.¹¹⁸² The development of arthritis in certain cases of meningococcic meningitis was not prevented, nor once established, was its course materially altered by penicillin (Rosenberg and Arling).

POSTSCARLATINAL RHEUMATISM

In most cases postscarlatinal rheumatism is now generally recognized as being identical with rheumatic fever (Bradley; Watson, Rothbard and Swift¹⁶⁸⁵).

Among 110 naval personnel with scarlet fever were 22 with pronounced electrocardiographic changes comparable to those seen in rheumatic fever: 19 had clinical manifestations of rheumatic fever. As a reaction to one or more immunizing doses of scarlet fever toxin 181 nurses developed articular pains. Among them, as compared to a control group who did not develop such reactions, there was a higher incidence of past and subsequent rheumatic fever and of rheumatic carditis (Rhoades and Afremow).

RAT BITE FEVER (HAVERHILL FEVER; SODOKU)

Much evidence suggests that a similar clinical syndrome (rat bite fever) may result from infection with either the *Spirillum minus* (Sodoku or Japanese rat

bite fever) or *Streptobacillus moniliformis* (Haverhill fever).^{225, 1955, 1965} The clinical,^{22, 1010, 1497, 1955} bacteriologic and laboratory features²²⁵ of the two types of infection were differentiated.

Haverhill Fever. This disease due to *Streptobacillus moniliformis* is the more common form of rat bite fever but may occur without the bite of a rat or other animal. With special media²²⁵ positive blood cultures for the *Streptobacillus* have been obtained.^{22, 219, 901, 943, 1476, 1893, 1955} The agglutination test for *Streptobacillus moniliformis* is a supplemental diagnostic procedure.^{103, 225, 781, 1068} The bacteriology of the *Streptobacillus* and its relation to the pleuropneumonia-like organism of Klieneberger were considered (Brown and Nunemaker²²⁵). Acute arthritis occurred in 12 of 20 collected cases²²: in three cases it lasted 53 days, eight months and more than two years respectively. Chief visceral lesion in a fatal case of Haverhill fever was focal myocarditis; sulfadiazine had been of no value (Blake, Horstmann and Arnold).¹⁵¹ But penicillin is effective. Of 86 mice infected with this *Streptobacillus*, all of 43 treated with penicillin, but only one of 43 not so treated, survived (Heilman and Herrell). Patients with this infection treated with penicillin have all recovered promptly.^{22, 219, 809, 943, 1476, 1893}

Sodoku. This form of "rat bite fever" was transmitted by the bite of a kitten¹⁷⁶² and a squirrel.⁴³³ The *Spirillum minus* was identified by direct darkfield examination of venous blood¹⁴⁸⁸ and of material from the wound.²⁵⁶ A diagnosis of Sodoku is usually made by inoculating noninfected mice and guinea pigs with patient's blood or tissue from the lymph node.^{110, 700, 1336, 1794, 1955, 1965} The Weil-Felix agglutination was positive in experimental rat bite fever due to *Spirillum minus* but agglutination of "Proteus OXR" was not demonstrated in human infections.

Arthritis rarely occurs in this type of rat bite fever. Unusual "gummatoid lesions" of Sodoku within muscles and periosteum were described (Vakil; Patel). [Laboratory confirmation of the clinical diagnosis was lacking.—Ed.] Necropsy findings in an infant 11 days old with *Spirillum minus* infection and bronchopneumonia were given.⁷⁰⁰ Penicillin is effective against the *Spirillum minus*: 25 experimentally infected mice were free of infection one day after treatment, but in the blood of 25 infected untreated mice spirilla were present during 37 days of observation (Heilman and Herrell). No case of *Spirillum minus* infection of humans treated with penicillin was reported.

RARER FORMS OF SPECIFIC INFECTIOUS ARTHRITIS

With Variola (Smallpox). Arthritis resulting from smallpox infection (Narasimhan) or vaccination (Kini and Kesavaswamy) was observed. Frank osteomyelitis and suppurative arthritis followed secondary pyogenic infection of the pustules in several cases. Juxta-articular and diaphyseal osseous lesions specifically due to the smallpox virus also were described: aseptic necrotic foci in shafts of long bones at the metaphyseal or epiphyseal ends of bones, causing arrest in growth of bone and in some cases bony ankylosis. Absorption of the epiphysis in other cases resulted in extensive deformity, but fair residual motion was preserved.

"Dysenteric Arthritis." Five cases occurring six weeks to eight months after the subsidence of bowel symptoms were described (Bonnin and Kay). The arthritis was presumably related to a "carrier" infection of the bowel with Flexner's *Bacterium dysenteriae*. Eradication of the latter infection resulted in full recovery. [Culture and examination of the synovial fluid were not done in any of

these cases. Hence the type of joint disease present remains in doubt.—Ed.] Sulfonamide was considered ineffective (Bauer, Ropes and Short).

Granuloma Inguinale and Lymphogranuloma Inguinale. Concerning these two different diseases confusion exists because of the similarity in the "ill-advised terminology"¹⁴⁹² and because of certain superficial clinical resemblances. But the causes, clinical course and complications of the two conditions are different.^{697, 1492}

1. *Granuloma Inguinale; Granuloma Venereum.* This is primarily a disease of the skin and subcutaneous tissues, usually of the inguinal region, caused by Donovan (not Leishman-Donovan) bodies. Despite its name it is not a venereal disease. Only occasionally does secondary nonspecific involvement of adjacent lymphatics occur. Systemic reactions and articular manifestations are rare or at least rarely mentioned. However, granuloma inguinale may be a systemic as well as a local disease, and Lyford, Scott and Johnson^{1137, 1564} reported a case of polyarthritides (ulceration of many joints, widespread destruction of bones) in which Donovan bodies were found in articular tissues and bone, also a second case with involvement of two vertebrae and a hip joint communicating with sinus tracts presenting in the inguinal regions. In these cases the onset of migratory polyarticular pain, swelling and effusions was insidious. At one stage disease in the joints resembled "typical rheumatoid arthritis," but months later articular swellings ruptured through skin leaving a granulating ulceration. An elbow was explored; synovia was thickened and friable, but cartilages were "clean and smooth." Articular tissue contained Donovan bodies in macrophages, and large numbers of plasma cells in exudate.

Orthodox treatment was discussed (Greenblatt⁶⁹⁷; Root¹⁴⁹²).

2. *Lymphogranuloma Inguinale; Lymphogranuloma Venereum; Lymphopathia Venereum.* This venereal disease, due to a filtrable virus, is primarily one of local (generally inguinal) lymphatics and surrounding connective tissue with secondary involvement of overlying skin and often constitutional and systemic manifestations including arthritis and anorectal strictures. A specific skin reaction to an antigen made from material aspirated from bubo (Frei test) occurs. The primary lesion is usually genital; the second stage comprises acute lymphadenitis (bubo); the tertiary (chronic) stage involves chronic granuloma, lymphatic progression and secondary infection to distant sites including joints ("exudative arthritis") and rectum (strictures) (Greenblatt; Root).

Among the constitutional evidences arthritis was prominently mentioned.⁸²⁷ A case with chronic arthritis involving "nearly all joints, without causing much deformity" was described.¹⁵³⁸ [No further details.—Ed.] Hickam⁸¹⁰ described articular manifestations under three categories: 1. Migratory arthralgia, usually fleeting, without objective joint changes is common in early weeks of infection. 2. Acute polyarthritides, painful swelling, redness and increased heat may accompany early or later stages of the disease. Ankles, hips, elbows and wrists are most often affected. The arthritis disappears rapidly without residues. Sometimes acute migratory arthritis may be evoked by a Frei test. 3. Chronic recurrent polyarthritides with effusions, in the later stages of the disease without deformity or functional impairment may occur. In this stage also effusions may follow the Frei test.

General articles appeared without special reference to joints,^{135, 697, 698, 950, 1152, 1194, 1987} also studies on the diagnostic value of laboratory tests.^{361, 685, 917, 1486} Treatment of the various stages and of nonarticular complications was discussed.^{206, 331, 697,}

698, 827, 920, 1024, 1338, 1573 Sulfonamides (sulfathiazole or sulfadiazine) were the drugs of choice. Sulfonamides combined with Frei antigen were considered of special value by some (Costello and Chen). Penicillin was ineffective (Mann).

Miscellaneous. *Hemophilus influenzae* was recovered from the knee of an infant 15 months old. Suppurative arthritis developed on the second day of an acute respiratory infection (Bercovitz). Suppurative periartthritis of the shoulder in an infant due to *Bacillus suispestifer* was described with a review of the literature (Guthrie). "Chronic arthritis" related to *Pseudomonas pyocyanea* infection of intestines was reported with "cure following autovaccine therapy" (Fiset). [Data presented did not prove an etiologic relationship.—Ed.]

MYCOTIC DISEASES OF JOINTS

Coccidioidomycosis; Coccidioidal Arthritis. Coccidioidomycosis, still rare, is of increasing interest as a cause of disease of bones and joints. The disease was originally confined to the San Joaquin Valley of California and most cases have originated in that state, 660 cases having been reported there up to 1941. But the disease has appeared in at least 16 other states, notably Texas and Arizona, and a new case was reported from Louisiana.¹⁵⁵¹ Infection occurs by inhalation of dust carrying endospores of *Coccidioides immitis*, the initial lesion being pulmonary. This may produce a symptomless infection, never recognized (as in most of the residents), or after an incubation period of eight to 21 days acute pneumonitis may develop which usually heals with fibrosis, occasionally with cavitation. Its relationship to coccidioidomycosis is generally not recognized and it is diagnosed "influenza" or "pneumonia."^{1407, 1947} During this pulmonary infection a relatively permanent skin sensitivity to the organism develops as indicated by positive coccidioidin test. The mortality rate of the acute pulmonary infection is less than 1 per cent. Of 736 soldiers stationed at Camp Roberts on the Western slope of the Coast Range Mountains of California, a region not previously known to be infected, 14 (2 per cent) had coccidioidomycosis (four symptomless; 10 with mild respiratory infection; Shelton¹⁵⁰⁵).

About 2 to 5 per cent of those who have acute respiratory symptoms demonstrate clinically an "allergic reaction" two to 20 days later, characterized by fever, "arthritis," articular and muscular pains, often conjunctivitis and erythema nodosum with or without erythema multiforme. This reaction has been termed "desert rheumatism," "desert fever," "valley fever," "San Joaquin fever." Joints are tender, painful and slightly swollen but no effusion occurs and after about a month symptoms disappear without articular residues.^{671, 672, 1501, 1925}

In the vast majority of cases nothing further develops but in about 0.05 to 0.3 per cent coccidioidomycosis becomes systemic,^{672, 1190, 1407, 1501} a progressive "secondary," disseminated infection known as coccidioidal granuloma, chronic granulomatous coccidioidomycosis, "San Joaquin Valley disease," "California disease."¹⁶³⁷ The rate of dissemination was "unbelievably high" (12 per cent) among the 49 cases of Willett and Weiss. Depending on the site or sites to which the fungus spreads granulomatous lesions occur in soft tissues, bones or parenchymatous organs commonly affecting meninges, bones, joints, muscles, skin and so forth.^{125, 401, 991, 1501, 1925} The mortality rate of "the dread granuloma" is 50 to 60 per cent; annually 46 such cases are reported in California (Shelton).¹⁵⁹⁵ In recent cases joints,^{280, 1154, 1100, 1501, 1641} multiple osseous sites including vertebrae, skin, liver and kidneys,^{1357, 1551} have been

involved. In one case both ankles were affected; in roentgenograms the lesions resembled somewhat tuberculous arthritis but biopsy revealed the fungus.¹⁵⁰¹ Granulomatous involvement of femur with secondary abscess of hip joint developed in one case (Martin).¹¹⁶⁰ In another case articular pains lasted several months after the acute pulmonary phase (Bush).²⁶⁷ In 79 of 256 collected cases of the chronic granulomatous phase, the joints were affected, ankles, knees and feet most frequently (Rosenberg, Dockerty and Meyerding¹⁵⁰¹). Joint involvement may be purely synovial, or synovial with subarticular destruction indistinguishable from tuberculosis (Benninghoven and Miller). The locations and nature of osseous lesions in more than 100 collected cases were discussed.¹²⁵

Treatment for the acute pulmonary disease with arthritis and erythema nodosum consisted of rest, salicylates¹⁶³⁷ or convalescent serum.⁶⁷¹ There is no known remedy for the chronic granulomatous phase^{1637, 1611}; penicillin and roentgen therapy were ineffective¹⁵⁰¹ against the coccidioidomycosis but penicillin may control secondary infections.⁴⁶⁰

Actinomycosis. A patient sprained his ankle; an actinomycotic abscess of the ankle developed and failed to heal after incision. Later the disease spread to heart and other organs. Diagnosis was first made at necropsy (Gose).

Actinomyces may enter the body via skin, lungs or intestines. From any primary focus they may reach vertebrae usually by direct invasion, occasionally by blood stream. In vertebrae a paravertebral phlegmon develops which may produce an abdominal lesion resembling tuberculous psoas abscess. Vertebral actinomycosis is rare; only about 50 cases have been reported, most of which were regarded as Pott's disease before necropsy. But roentgen findings are "characteristic if not definitely diagnostic": areas of destruction in all parts of the vertebra with surrounding sclerosis. Despite extensive destruction, vertebral collapse is rare; even then intervertebral disks are spared. Three cases were reported (Lubert).

The heart may be reached by metastasis or by direct extension, commonly from lung. Actinomycosis of heart may simulate rheumatic heart disease (Cornell and Shookhoff; Gose; Lidbeck).

Histoplasmosis. This chiefly affects the reticulo-endothelial system. Caused by the fungus, *Histoplasma capsulatum*, lesions occur notably in liver, spleen, lymph nodes, bone marrow and lungs. Fever, anemia, leukopenia, emaciation, enlargement of liver and spleen result. The fungi are found in cytoplasm of circulating monocytes, in tissue phagocytes and elsewhere. Presumably the first case in which joints were involved was noted by Key and Large.⁹⁹⁵ The case resembled tuberculous arthritis but tuberculin test and guinea pig inoculation were negative. The leg was amputated; 10 days later death resulted from pneumonia and cardiac failure. The diagnosis was not suspected until examination of synovial tissue revealed the Histoplasma.

RHEUMATIC FEVER

Incidence. Determination of the incidence of rheumatic fever is handicapped because the disease is generally not reportable. However, useful and reasonably accurate estimations were reported.

Keith⁹⁶⁵ estimated that rheumatic heart disease affects 0.10 to 2.08 per cent of British, 0.9 to 1.36 per cent of American and 0.36 to 3.92 per cent of Canadian, school children. In New York City from 1936 through 1938, 681 deaths from rheumatic

fever, or rheumatic heart disease, were recorded in children five to 14 years of age.¹¹⁵⁸ This number exceeded deaths from accidents for that age group and was two and one-third times greater than deaths from infantile paralysis, pulmonary tuberculosis, scarlet fever, measles, whooping cough and diphtheria combined. Martin¹¹⁵⁸ estimated that 1,000,000 people in the United States had rheumatic carditis which caused 40,000 deaths yearly at the average age of 30 years. The incidence of rheumatic heart disease in school children ranged between 0.7 and 1.0 per cent. Rheumatic fever with rheumatic heart disease was the leading fatal disease from the ages of five through 19 years.^{39, 1225, 1229} For each 100,000 men examined for selective service 340 were rejected with the main diagnosis of rheumatic heart disease (Rowntree). The actual incidence was much higher as many men were rejected for obvious defects who also had rheumatic heart disease; also, in many cases it was not detected at the initial examination. Fifty per cent of all men rejected for cardiovascular diseases had rheumatic heart disease. Shaffer found rheumatic heart disease in 1 per cent of 25,000 selectees. Levy, Stroud and White reported that of the men rejected because of heart disease, rheumatic heart disease was responsible for 51 per cent in Boston, 70 per cent in Chicago, 64 per cent in New York, 70 per cent in Philadelphia and 40 per cent in San Francisco. The Children's Bureau estimated that in this country 500,000 children are handicapped by rheumatic fever and rheumatic heart disease (Lenroot).

In England deaths from rheumatic fever declined from 23 per 1,000,000 (all ages) in 1939 to 12.1 in 1942 (Glover). In the United States the deaths from rheumatic fever and rheumatic heart disease in persons aged five to 24 years fell from 32.3 per 100,000 in 1917 and 1918 to 9.7 in 1943 (Metropolitan Life Insurance Company^{1227, 1228}). Each five-year period since 1922 has shown a lowered mortality rate and decrease in the percentage and severity of cardiac damage.¹¹

Predisposing Factors Governing Incidence. 1. *Geography and Climate.* Reports agreed that rheumatic fever is more common and severe in temperate than in warmer climates. The influence of geography and climate was investigated by three standard routines: (1) comparison of the incidence of rheumatic fever among comparable groups; (2) comparison of hospital admission rates, and (3) analysis of necropsy data. The opportunity to study the incidence of rheumatic fever in troops in various geographic areas during the past war added greatly to our knowledge of geographic incidence. Maps prepared from the Surgeon General's report¹⁴⁵⁴ showing the incidence of disease at different posts illustrated the marked difference in the frequency of rheumatic fever in the North as compared to the South. The Army Air Forces surveyed 40 posts scattered throughout the United States and found a strikingly high incidence of the disease in the Rocky Mountain area, Great Lakes area, and Midwest, with a low incidence along the Mexican border and Gulf of Mexico (Holbrook and van Ravenswaay^{855, 856}).

Climatic factors are exceedingly complex and comprise many other factors than latitude, as was illustrated by a study of the incidence of rheumatic fever in school children in three California cities with different climatic factors. In Eureka, a north California sea coast town with a fairly high rainfall but equitable temperature, the incidence of rheumatic heart disease among school children was 2 per cent; in Susanville, at an altitude of 4,268 feet with moderate rainfall, it was 1.1 per cent; in Redlands, with an altitude of 1,350 feet and relatively dry, it was only 0.38 per cent (Sampson, Hahman, Halverson and Shearer). Paul¹³⁴⁸ found 10 times as much rheumatic heart disease among Indian school children near the Canadian border as was present among Indian school children living near the Mexican border.

Although rheumatic fever and rheumatic heart disease are less frequent in the southern states and in the tropics, the incidence there is such that attention should be paid to the problem.^{285, 293, 734, 770, 1055, 1187, 1225, 1229, 1471, 1602, 1819, 1880, 1914}

Data on comparison of hospital admissions were summarized: The percentages

of children admitted with rheumatic fever or rheumatic heart disease were as follows: Philadelphia 5.8; Portland, Oregon 3.5; Cincinnati 2.7¹⁸⁹⁶; Dallas 0.8⁵¹¹; Los Angeles 0.69.⁴⁴¹ The percentages of total admissions to general hospitals for rheumatic fever or rheumatic heart disease were as follows: Galveston, Texas, 1930-1939, 0.2¹⁵²; Vizagapatan, India, six-year period, 3.5.^{1052, 1053} In Galveston rheumatic heart disease during 1930-1939 constituted only 2.1 per cent of total cardiac admissions (Decherd and Herrmann). These low findings contrast with those of Chavez³¹¹ in Mexico who reported that in charity cases rheumatic heart disease constituted 62 per cent and in private cases 41 per cent of the total cardiac cases. "These are tremendous differences for which some explanation must be sought."

Comparable necropsy studies, reported from various geographic areas, are summarized giving the incidence of rheumatic heart disease: in Boston 5.5 per cent (456 of 8,300 necropsies⁶³⁴); in Atlanta 3.5 per cent (61 of 1,754 necropsies³²⁰); in Galveston 0.9 per cent (22 of 2,463 necropsies¹⁵²); in New Orleans 0.63 per cent (102 of 16,121 necropsies²³¹).

Four times as much mitral stenosis was found in Atlanta as in New Orleans although the economic level of the patients in the two hospitals studied was comparable (Claiborne and Wolff³²⁰).

The incidence of rheumatic carditis among Denver high school girls was 16.3 per 1,000 (Wedum, Wedum and Beaghtler¹⁸⁹⁹). Denver was said to have the second highest death rate from rheumatic heart disease among the 25 largest American cities.

2. *Season.* In the temperate zone the greater prevalence of rheumatic fever in winter and spring was reaffirmed.^{1226, 1227, 1318, 1319} No seasonal variations occurred in India.¹⁰⁵²

3. *Social and Hygienic Factors.* The greater frequency of rheumatic fever among low income groups was again noted.^{378, 1159, 1264, 1348, 1349, 1360, 1503, 1906} The importance of crowding was stressed.^{1229, 1273, 1808, 1920}

4. *Family, Heredity and Constitution.* The familial tendency of rheumatic fever was again supported by Wilson and her colleagues^{1910, 1912}; its distribution followed the general laws of recessive mendelian inheritance. Others considered the familial factor important.^{276, 277, 1171, 1229, 1347, 1503} But some observers from various parts of the country found no significant familial incidence.^{721, 1052, 1006} The familial incidence was variously reported as being 5.7 (compared to 3.6 among controls),¹⁵³⁰ 7.6,³⁷⁹ 8.9⁴⁴¹ and 12 per cent.⁹⁰⁷

5. *Sex.* The incidence is essentially the same in both sexes, if chorea is excluded.^{351, 1055, 1318} The death rate among males is a fifth greater than among females (Metropolitan Life Insurance Company^{1228, 1229}).

6. *Age.* The peak incidence and average age of onset was at eight years^{351, 512, 721, 880, 925, 1158}; currently the oldest patient with an initial attack of acute rheumatic fever was 61 years of age (Rakov and Taylor¹⁴²⁹) and the youngest was a newborn infant 10 days old (Denenholz and Rambar).

7. *Race.* As to racial differences opinions varied. The incidence of rheumatic fever and carditis was about the same among Negroes and whites in New Orleans,²³¹ also in Louisville, Kentucky,¹⁹⁰⁶ greater among the Negroes in Cincinnati,¹⁸⁹⁷ and less among the Negroes than whites in Philadelphia.⁵⁰⁶

GENERAL SYMPTOMATOLOGY AND RELATIVE INCIDENCE OF VARIOUS MANIFESTATIONS OF RHEUMATIC FEVER

Of 1,487 cases of rheumatic fever in Chicago Gibson⁶³⁰ noted polyarthritides in 983, chorea in 581, rheumatic nodules in 156, carditis in 864. Other rheumatic manifestations affected 74 per cent of the polyarthritic patients, 56 per cent of the choreic patients, all of those with rheumatic nodules and 84 per cent of those with carditis.

Of 583 children with rheumatic heart disease the initial manifestation was acute carditis in 8 per cent, polyarthritis in 60 per cent, chorea in 20 per cent, myalgia and joint pains in 10 per cent, insidious carditis in 9 per cent (Ash⁴¹). Pain in a joint of the lower extremity was the initial symptom in most of Kimbro's 100 cases. Sometimes this was so mild that the patients had been referred for flatfeet. In a study of 1,754 necropsies of rheumatic heart disease a past history of articular involvement was noted in only 29 per cent (Claiborne and Wolff). But Shapiro¹⁵⁹⁰ obtained a history of arthritis in all but 2 per cent of his cases, and Martin¹¹⁵⁸ failed to obtain a history of chorea or arthritis in only 14.7 per cent. The importance of rheumatic nodules was emphasized.^{68, 397, 1739} All of the 167 patients with rheumatic fever with nodules studied by Hayes and Gibson presented some other manifestation of rheumatic fever and 163 had definite signs of heart disease.

PATHOLOGY OF RHEUMATIC FEVER: GENERAL CONSIDERATIONS AND CLINICOPATHOLOGIC DATA

Cardiovascular System. The incidence of rheumatic stigmata in hearts presumably normal, nonrheumatic and obviously free of gross valvular lesions was found on microscopic examination by Hall and Anderson to be surprisingly high. In 90 per cent of 112 such grossly normal hearts from persons without clinical evidence of rheumatic infection or valvulitis, rheumatic myocardial lesions were found in close proximity to mitral valves. All the well-known rheumatic stigmata were "abundantly present" including Aschoff bodies in 30 per cent.

[These figures are indeed surprising unless we are to believe that 30 to 90 per cent of all hearts show (at least microscopic) evidence of rheumatic carditis. Otherwise these lesions will have to be regarded as nonspecific tissue responses to various insults, not necessarily to the "rheumatic virus."—Ed.]

The relationship between Aschoff bodies and rheumatic activity was noted by Console who studied 98 cases in which endocarditis or pericarditis was found at necropsy and in which there was a history of rheumatic fever. Aschoff bodies were found in all in which death occurred in the first decade of life, in 64 per cent in the second decade of life, and in 11 per cent of those in later life. When Aschoff bodies were found, the last attack of polyarthritis preceded death by five months or less. In three cases there was no history of rheumatic fever despite the presence of Aschoff bodies.

Stokes-Adams attacks in a child with insidious rheumatic pericardial effusion¹⁷¹⁶ and intermittent bundle-branch block in a case of acute rheumatic fever were reported.⁷⁸⁷ In cases of chronic rheumatic heart disease auricular fibrillation may be due to substitution of the auricular smooth muscle for striated cardiac muscle.⁸⁸⁸

Of 2,476 persons with rheumatic valvular disease rejected by draft boards in five cities and studied by special boards of review, 750 had mitral regurgitation alone, 750 had mitral stenosis alone, 208 had aortic regurgitation alone, 72 had aortic stenosis alone, 628 had combined mitral and aortic disease; 68 had unspecified lesions (Levy, Stroud and White¹⁰⁰⁰).

Pericarditis is an ominous sign according to Ash⁴²; 75 per cent of 553 children with rheumatic pericarditis who were observed for 9.6 years died.

The presence of occasional upper respiratory infections, articular symptoms and high antistreptolysin titers in 10 persons less than 30 years of age who died of myocardial infarctions suggested to Weinstein that some infarctions are of rheumatic origin. The possible rheumatic origin of certain coronary lesions and of angina pectoris in young persons was noted also (Ernstene and Schneider; King¹⁰⁰⁴).

Joints. No new data appeared. [It is unfortunate that so little is known about the pathology of joints in rheumatic fever. Surely enough patients die either during acute rheumatic polyarthritis or sufficiently soon thereafter that much data could be learned by examination of articular tissues as well as heart at necropsy. Why are pathologists so loathe to invade joints when they invade without compunction the more "sacred" heart and brain?—Ed.]

Lungs and Pleura. There is "no specific rheumatic pneumonia" ⁵³⁰ according to some but others disagreed.¹²⁰² The "Masson body" is not specific ⁸²³ but was believed to be due to capillary damage with altered permeability. The following were noted: hemoptysis in 10 per cent of cases of rheumatic heart disease, and pulmonary arteriosclerosis.¹⁹⁵⁸

Skin and Mucosa. Erythema marginatum ³⁹⁷ and erythema multiforme each occurred in 1.9 per cent of rheumatic patients; the presence of erythema multiforme was considered a poor prognostic sign.¹⁷³⁹

Nervous System. The relation of the nervous system to, and the late cerebral sequelae of, rheumatic fever were again discussed (Bruetsch ²²⁸).

Rheumatic carditis occurs with unusual frequency in the mentally ill but its incidence differs somewhat with the type of mental illness: 9 per cent in cases of schizophrenia; only 1.7 in cases of dementia paralytica. Unsuspected rheumatic carditis, "rheumatic encephalitis," cerebral embolism, and cerebral obliterative endarteritis often is revealed at necropsy on psychotics.^{229, 486} Meningoencephalitis, with an inflammation "compatible with that of rheumatic fever" was noted in a case of fatal, proved rheumatic fever.⁸⁴²

In 29 cases of rheumatic carditis (in 59 per cent of which Sydenham's chorea had occurred) convulsive disorders presumably rheumatic developed.⁵⁷⁷ The term "rheumatic epilepsy" was applied by Bruetsch ²²⁷ to convulsive seizures following rheumatic fever or chorea, and for epilepsy associated with chronic rheumatic valvulitis.

Chorea and its relationship to rheumatic fever will be discussed separately.

Kidneys. Rheumatic patients with renal insufficiency and necropsy findings of focal glomerular nephritis and arteritis, and diffuse obliterative renal vascular disease were noted (Hutton and Brown).

Eyes. "There is no ocular pathologic change pathognomonic of rheumatic fever" (Rudolph ¹⁵¹⁷).

Testes. Trasoff and Goodman ¹⁸⁰⁷ reported a case of "rheumatic orchitis" associated with rheumatic pericarditis. [There is no proof of the rheumatic origin of the orchitis.—Ed.]

LABORATORY DATA IN RHEUMATIC FEVER

Electrocardiogram. Abnormalities were reported in from 50 to 77 per cent of cases of rheumatic fever ^{287, 1327, 1910} and in 39 per cent of cases of Sydenham's chorea.⁸⁰⁷ Carotid sinus pressure produced increased impairment of the atrio-ventricular conduction time in 12 of 16 patients with active rheumatic carditis. Administration of prostigmine augmented the response.⁷¹² Wendkos suggested the intravenous use of ergotamine tartrate (gynergen) to increase the diagnostic precision of the electrocardiograph in rheumatic fever. Atropine is of no help in distinguishing P-R intervals prolonged by vagotonia from those prolonged by rheumatic fever, because atropine reduces the P-R time equally in both.¹⁴⁴⁵

Sedimentation Rate of Erythrocytes. Formol Gel Test and Weltman Reaction. The sedimentation rate is the most sensitive test of rheumatic activity.^{322, 650, 1013, 1214, 1879} It is seldom increased in chorea unless other rheumatic manifestations are also present.^{120, 322, 1590} Nine of Harris' ⁷⁷⁸ 400 patients with rheumatic fever continued to have high sedimentation rates long after all other evidences of activity of the disease had subsided. An abnormal Weltman reaction, especially a shortened coagulation band, was found by Scherlis and Levy to be more frequently associated with rheumatic activity than was an elevated sedimentation rate. Otherwise the tests were statistically about equal. Formol gel tests were less sensitive and of less value in determining rheumatic activity than sedimentation rates.^{270, 1013}

Blood Counts. The nonfilamented neutrophile count was of less value than the erythrocyte sedimentation rate.¹⁸⁷⁹

Capillary Resistance. This was found generally to be low in 150 rheumatic children (Brown and Wasson). It varied with changes in temperature and barometric pressure.

Blood Salicylate Level. A method for the determination of salicylic acid in plasma was described.^{216, 330}

Serum Proteins. Changes in serum protein in scarlet fever and rheumatic fever were qualitatively similar.⁴⁷⁵ Albumin-globulin ratios were sometimes inverted.¹⁶²⁷

Blood Sugar. Following tolerance tests, sugar curves suggesting hyperinsulinism were found in 11 cases of rheumatic fever (Abrahamson⁵).

RELATIONSHIP OF RHEUMATIC FEVER TO OTHER DISEASES

Rheumatoid Arthritis. The relationship of rheumatic fever to rheumatoid arthritis has been the subject of conflicting reports. At necropsy evidence of rheumatic heart disease was found in 16 (53 per cent) of 30 rheumatoid patients, according to Baggenstoss, Rosenberg and Hench^{53, 54, 1500} who concluded: "This evidence suggests ever more strongly that rheumatoid arthritis and rheumatic fever are in some manner closely related." A similar conclusion was made by Young and Schwedel who found "rheumatic heart disease" in 25 (66 per cent) of 38 necropsies in cases of rheumatoid arthritis. But Bennett¹²² arrived at quite a different conclusion from his study of necropsies on 101 patients with rheumatic fever and 48 patients with rheumatoid arthritis: "It is apparent that the usual anatomical changes observed in rheumatoid arthritis differ so markedly from those of rheumatic fever that one must infer that the pathogenesis of the observed lesions is different."

[This topic is discussed further under "Pathologic Characteristics of Rheumatoid Arthritis" and "Relationship of Rheumatoid Arthritis to Rheumatic Fever."—Ed.]

Subacute Bacterial Endocarditis. The recurring arthralgia and arthritis seen in some patients with endocarditis caused by *Streptococcus viridans* were considered as being due to complicating acute rheumatic fever or the "general toxemia caused by bacterial endocarditis." The latter was held more likely in view of the unusual clinical features and the failure to respond to the usual forms of therapy for rheumatic fever (Christian³¹⁷). [Many patients dying of subacute bacterial endocarditis are found to have coexisting rheumatic fever at necropsy.—Ed.]

In 25 per cent of 452 fatal cases of rheumatic heart disease postmortem evidence of bacterial endocarditis was noted (Gelfman), and rheumatic carditis was present in 90 per cent of 174 consecutive adult patients with subacute bacterial endocarditis (Christian³¹⁶). The rheumatic heart lesion was called the "determinative background for bacterial endocarditis."

Erythema nodosum. No evidence supported the theory that erythema nodosum is a manifestation of acute rheumatism. Perry¹³⁸² found only 10 cases of erythema nodosum in more than 1,000 patients with acute rheumatism.

Miscellaneous Diseases. The relationship of rheumatic fever to glomerulonephritis,¹⁵⁷² scarlet fever,^{203, 1885} scarlet fever immunization,¹⁴⁵⁵ rubella¹²⁸¹ and fibrositis⁸⁷⁹ was discussed.

DIFFERENTIAL DIAGNOSIS IN RHEUMATIC FEVER

Data to be considered in the diagnosis of rheumatic fever were tabulated by Jones⁸²⁴ who listed five major manifestations (carditis, arthralgia, chorea, subcutaneous nodules and febrile rheumatic recurrences) and seven minor manifestations (fever, abdominal pain, precordial pain, rashes, epistaxis, pulmonary findings and laboratory data). Any single major manifestation with at least two minor manifestations would place the diagnosis on reasonably safe grounds. Similar criteria were emphasized by Barnes and by Griffith.

Hansen^{750, 751} compared the admission diagnosis with the final diagnosis in 271 cases of supposed rheumatic fever among children. One-third of the initial diagnoses were incorrect. The most probable causes of error in the order of frequency were: abdominal pain with possible appendicitis, acute anterior poliomyelitis, acute osteomyelitis, skin eruptions and nephritis.

The abdominal pains of rheumatic fever were discussed.^{35, 129, 1450} There are no abdominal signs which warrant clear-cut differentiation between suppurative appendicitis and rheumatic "pseudo-appendicitis." But estimations of the sedimentation rate are helpful as the rate tends to be normal in suppurative appendicitis but sharply increased in rheumatic pseudoappendicitis (Langmann). Differentiation between nonrheumatic "growing pains" and rheumatic joint pains was again discussed.^{41, 282, 579, 650, 1590} Acute rheumatoid arthritis, Still's disease, disseminated lupus erythematosus, brucellosis, coccidioidomycosis and subacute bacterial endocarditis occasionally demand the utmost in diagnostic acumen in making a differential diagnosis.^{76, 750, 751, 924, 1451} A case of actinomycosis of the heart simulating rheumatic fever was described.³⁸⁹

COURSE, PROGNOSIS AND END RESULTS OF RHEUMATIC FEVER

The disease was severe in a third, moderately severe in a half, and mild in a fifth of 54 Boston cases (Bland). The average duration of active infection was eight months, but three patients required rest in bed for two to two and one-half years. Of 553 children with rheumatic fever followed by Ash⁴¹ for an average of nine years 71 per cent showed signs of heart disease at one time but because of regression of such signs a diagnosis of organic valvulitis was eventually made in only 64 per cent. Twenty-six per cent had died. First attacks of rheumatic fever are more likely to cause carditis in children than in adults.^{40, 957, 966, 1462, 1590} Delice, Dodge and McEwen found residual cardiac damage in 7 per cent of 67 adults and in 28 per cent of 78 children. The incidence of heart disease varies also with the clinical type. Children whose disease began with acute carditis had the highest initial mortality: 65 per cent were dead in 10 years.^{41, 42}

Records of 3,129 patients with fatal rheumatic heart disease were analyzed by Cohn and Lingg. The average duration of disease was about 13 years. Fifty per cent died within nine years after onset, 25 per cent lived more than 17 years and 10 per cent for 30 years or more. Whereas Cohn and Lingg analyzed only fatal cases, Martin¹¹⁵⁸

studied a group of 1,438 children with rheumatic heart disease; 30 per cent were dead after 20 years, 43 per cent of the deaths occurred within five years of the initial rheumatic attack; more than two-thirds succumbed before the age of 16 years.

In a follow-up of 1,000 patients with rheumatic fever Jones and Bland found that at the end of the 10 years 31.3 per cent had no detectable heart disease; 47 per cent had some degree of rheumatic heart disease; 20.3 per cent had died, mostly as the result of recurrent rheumatic fever; follow-up data in 1.4 per cent were inadequate. Of the 1,000 patients, 64.8 per cent were able to lead relatively normal lives 10 years after the onset of rheumatic fever. [An interesting and reassuring study.—Ed.]

Studying 499 rheumatic patients during 5,677 "person-years" Wilson and Lubschez found only two factors which influenced the risk of future recurrences: the age of the child and the interval of time elapsing since the last attack. It was calculated that the risk of recurrence during the year immediately following a major episode is 38.7 per cent compared to 11.2 per cent in the year after one year of freedom. Similar figures were presented by Ehlertsen, but Cohn and Lingg in their analysis of more than 3,000 patients concluded that recurrences are most prevalent before puberty regardless of the interval of freedom.

Auricular fibrillation in cases of rheumatic heart disease which had lasted 12, 13 and 15 years was reported (Kosamann and Connor). Other interesting clinical and statistical reports cannot be reviewed here.^{40, 42, 153, 221, 397, 650, 656, 934, 966, 1176, 1769, 1777, 1921}

The important but well-known signs of activity and quiescence of rheumatic infection were reviewed.^{87, 153, 282, 966, 1777, 1881, 1971}

ETIOLOGY AND PATHOGENESIS OF RHEUMATIC FEVER

Factor of Infection. 1. Streptococcic Infection. Further evidence favored hemolytic streptococci as a direct, or indirect, cause of rheumatic fever.^{547, 693, 694, 878, 1174, 1176, 1455, 1680, 1919} The great tendency of upper respiratory infections to induce rheumatic attacks^{153, 691, 1050, 1768} and the close relationship of epidemics of hemolytic streptococcic infections and rheumatic fever in the armed forces were noted.^{331, 691, 855, 912, 1969}

The carrier rate for Group A hemolytic streptococci in well troops was shown by Van Ravenswaay to parallel rather closely the incidence of rheumatic fever. Of 38 clear-cut and nine questionable rheumatic occurrences observed by Kuttner,¹⁰⁴⁸ all 47 followed streptococcic upper respiratory infections. The relationship of postscarlatinal arthritis and carditis to rheumatic fever was noted: in 19 of 110 cases of scarlet fever abnormal electrocardiograms were noted during convalescence (Watson, Rothbard and Swift¹⁸⁸⁵). Only eight of the 19 patients had definite clinical attacks of rheumatic fever but the authors believed that, following their streptococcic infection, all suffered from the same fundamental tissue injury characteristic of rheumatic fever. Rheumatic fever may long remain active in a subclinical form; respiratory infections are important only in such cases; in really inactive cases respiratory infections were not followed by recurrences (Juster⁹³⁷). Thomson and Glazebrook did not find a definite parallelism between the occurrence of rheumatic fever and epidemics of tonsillitis in a semiclosed community. Green⁶⁹³ recovered hemolytic streptococci from the valves with microscopic lesions of rheumatic fever in eight of nine cases.

Serologic reactions in cases of rheumatic fever continued to suggest a relationship

to hemolytic streptococci. Precipitin tests such as antifibrinolysin and antistreptolysin reactions tended to be the same in cases of rheumatic fever as in cases of proved hemolytic streptococcal infection.^{172, 315, 692, 1101, 1266} Autoantibodies to human heart were present in the blood of 75 per cent of a group of patients with acute rheumatic fever (Cavelti).

Experimental myocardial lesions induced by *Streptococcus viridans* were not those of rheumatic fever.⁷⁰⁹

2. *Other Infections.* Copeman³⁷⁰ described cases in which the infection preceding rheumatic fever was not streptococcal. Dysentery, sand fly fever and malaria at times seemed to precipitate rheumatic fever. An outbreak of influenza did not precipitate rheumatic recurrences in children.^{1050, 1451} No relationship was found between acute rheumatism and epidemics of rubella, measles, chickenpox, common cold and diphtheria (Green⁶⁹¹).

3. *Virus Theory.* The question continues to be raised whether an unidentified virus may not be the direct cause of rheumatic fever, acting in association with hemolytic streptococcal infections.^{1050, 1077} Green⁶⁹³ considered the evidence not positive.

4. *Experimental Transmission of Rheumatic Fever.* In what was believed to be the only study of its type on record Copeman³⁸⁰ reported the probable transference of rheumatic fever from a patient with the disease to three of five volunteers by injecting intravenously 5 c.c. of the patient's blood into each volunteer. The blood was transferred on the fourth day of the patient's illness to five volunteers. Mild attacks of "rheumatic fever" developed in two of them after 24 hours, and pain in the shoulder muscles without pyrexia three days later in another. Blood from the two patients contracting mild rheumatic fever was pooled on the third day and again passed on to four volunteers. One of the four had an attack of febrile fibrositis on the second day. Blood from the more severely affected of the first two patients was again transferred on the seventh day of illness to four more volunteers. In one of these painful generalized fibrositis developed which six weeks later seemed likely to become chronic. Copeman³⁸⁰ stated that these studies were not sufficiently controlled but that an infective agent appeared to be present in the blood of the original patient which was capable of transference to others.

[If this work can be repeated and confirmed, it will go a long way to support the virus theory.—Ed.]

Factor of Allergy and Anaphylaxis. To cutaneous injections of purified M proteins of 40 types of hemolytic streptococci 65 per cent of normal children and 83 per cent of rheumatic children gave a positive reaction (Taran, Jablon and Weyr^{1770, 1771}). Struck by the relationship of periarteritis nodosa to sensitivity states, Rich and Gregory^{1458, 1461, 1462} produced in rabbits, with the antigen horse serum, lesions considered identical with those of that disease. By the same means Rich¹⁴⁵⁸ produced in 19 of 51 rabbits changes in the heart which he regarded as typical of rheumatic fever: focal alterations in collagen; nonspecific inflammatory lesions in valves, endocardium, myocardium and pericardium; valvular nodular projections of swollen and degenerating collagen with damaged overlying endothelium; small foci of myocardial necrosis and myocardial lesions with the basic characteristics of Aschoff bodies. Such changes did not occur spontaneously in hundreds of other rabbits. Rich¹⁴⁵⁸ concluded that rheumatic fever is an allergic disease with a native individual difference

in reactivity which determines not only whether a hypersensitive reaction occurs in a given sensitized individual on contact with the antigen but also in what tissue the hypersensitive reaction occurs. Robinson^{1481, 1482, 1483} was unable to confirm Rich's¹⁴⁵⁸ work, finding that horse serum alone did not produce a carditis like that reported by Rich.¹⁴⁵⁸ He was able to produce many lesions typical of streptococcic disease of human beings and some cardiac lesions resembling those found in human rheumatic fever by injecting sterile erythrogenic filtrate of NY-5 hemolytic streptococci into young albino rabbits. Clawson failed to confirm the work of either Rich or Robinson and found no evidence favoring the theory that streptococcic toxin acts directly or by an allergic reaction on valves. Neither was he able to produce rheumatic heart lesions from hypersensitiveness or serum sickness alone. But rats infected intracardially with *Streptococcus viridans* or hemolytic streptococci developed acute rheumatic-like endocarditis or bacterial endocarditis or both. Clawson concluded that acute rheumatic endocarditis and bacterial endocarditis occur only as a response to a direct valvular infection with bacterial cells. Other experimental work was reported.^{597, 1077, 1086, 1087} Loewenstein^{1118, 1119} cultured tubercle bacilli from the blood in 69 per cent of 412 cases of rheumatic fever and concluded that rheumatic fever is due to hypersensitivity to tubercle bacillus. [See the discussion on "Tuberculous Rheumatism."—Ed.]

Factor of Vitamin Deficiency. The diet of 50 patients with rheumatic fever was deficient in vitamins A and D, calcium and phosphorus.¹³⁵⁸ Irrespective of its previous concentration, that of vitamin A in plasma falls with the onset of rheumatic fever but the carotene content is not altered.¹⁵⁸⁷

Patients with frank avitaminosis B in India rarely develop rheumatic fever (Kutumbiah).

The subnormal plasma content of vitamin C in rheumatic fever and the possible influence of vitamin P was discussed (Rinehart).

Hormonal Factors. A type of hormonal imbalance is a predisposing or causative factor in rheumatic fever, according to Tormey, Woods and Gallagher.¹⁸⁰³ This imbalance, present in certain persons at birth, "is created by disequilibria among the derivatives of the polycyclic hydrocarbon cyclopentanoperhydro-phenanthrene."

Physical Factors. Rheumatic fever may begin within a few days of trauma; the traumatized joint may be the first affected (Glazebrook and Thomson⁶⁵⁷). Weight-bearing joints are often first affected (Couper; Kimbro). Physical factors (exposure, cold, wet, excessive fatigue) are important predisposing factors; cases in which physical factors of extreme degree alone appear to be responsible were reported (Copeman³⁷⁹).

Conclusions on Etiology. There was considerable agreement that hemolytic streptococcic infections are related to rheumatic fever, but the mechanism of action of hemolytic streptococci remains unknown (Paul¹³⁴⁷).

[From data available it appears that rheumatic fever usually occurs in a susceptible person following a hemolytic streptococcic infection in a climate having the necessary meteorologic factors. The individual's environment with regard to housing, working conditions, financial status, warmth, exposure, fatigue and so forth is also an important factor in increasing or decreasing his liability to rheumatic fever. But the exact cause of the disease remains unknown.—Ed.]

TREATMENT OF RHEUMATIC FEVER

Rest. For the acute phase of rheumatic fever complete rest is "the one indispensable measure"; it should be continued until all evidences of activity of the disease have disappeared.^{41, 153, 252, 691, 847, 1055, 1511, 1769}

By superimposing serial roentgenograms and noting variations in cardiac size Taussig and Goldenberg were able to prove more precisely the value of rest. A rheumatic heart may (1) grow in size normally, (2) after a period of enlargement, remain stationary in size while the chest grows or (3) enlarge progressively. If adequate rest has been provided during the acute phase, in most cases the heart will not enlarge progressively. However, cardiac breakdown is not due to overexertion but to reinfection (Watkins¹⁸⁸¹). Unnecessary, anxious long periods of rest will produce cardiac neurosis.^{532, 999}

[To avoid this needless complication the War Department urged medical officers not to overdo in the matter of resting convalescent rheumatic soldiers but to encourage the rheumatic soldiers to resume graduated physical activity as soon as the active disease subsided. The War Department's memorandum thereon¹⁸⁷⁰ will be instructive to civilian physicians.—Ed.]

Salicylates. These remain the most valuable remedy and are almost specific for relieving symptoms. Differences of opinion exist as to the dosage required and as to the relative merits of oral or intravenous administration. This old controversy (Mendel, 1904) was recently reopened by Coburn³³⁰ who reported a method for determining concentration of salicylates in blood and expressed his belief that acute rheumatic fever could be rapidly suppressed if, by the intravenous administration of salicylates, concentrations were maintained at about 35 mg. per 100 c.c. of plasma. In 38 patients so treated "valvular heart disease" did not develop but in 21 (33 per cent) of 63 patients given orally smaller doses of salicylates signs of "heart disease" developed.

Preliminary approval of the intravenous use of large doses to obtain high blood levels was given by some,^{650, 691, 999, 1055, 1105, 1969} but subsequent workers were not able to confirm the value of high blood levels.

No difference was noted in the effect on sedimentation rates, and the final percentages of patients who had cardiac damage were identical in all of three groups of patients of Warren, Higley and Coombs treated thus: small oral doses of salicylates sufficient to control symptoms in 88 patients; larger oral doses to maintain adequate levels in the plasma in 50 patients; large doses given intravenously by Coburn's technic. Similar disappointing experiences were reported by others.^{260, 667, 1275, 1902, 1903} The intravenous use of large doses of salicylates and the maintenance of high blood levels did *not* give results superior to those from the oral use of standard doses. The former did not control or prevent recurrences, hasten the return of sedimentation rates to normal, hasten materially the subsidence of the acute phase of rheumatic fever, or prevent the development of carditis.

The effect of salicylates on enzymes and metabolic processes in animals was studied in detail (Lutwak-Mann). Certain notable changes in liver glycogen occurred. Urinary metabolites of sodium salicylate also were studied (Kapp and Coburn).

1. Toxicity of Salicylates. Besides having no advantage over the oral use, the intravenous use of salicylates was condemned as dangerous.^{1105, 1591, 1874, 1903, 1969}

Even though plasma levels were the same, toxic reactions occurred six times as often in patients treated intravenously as in those treated orally by Warren, Higley and Coombs,¹⁸⁷⁴ but in most cases reactions were mild: nausea, occasional vomiting, tinnitus, colored vision. With the highest blood levels hyperventilation, acute maniacal delirium and pustular acne sometimes developed.

When large doses of salicylates were given orally to McEachern's¹¹⁹⁵ patients,

discomfort (usually only mild nausea or tinnitus) developed in less than 25 per cent but when salicylates were given intravenously, marked symptoms developed in nearly all 37 cases. These consisted of vomiting, shaking chills in 10 cases and in six cases acute psychosis, incoherent speech, disorientation, rapid pulse, acute air hunger. One death occurred.

Other fatal reactions were reported. Salicylate toxicity produces respiratory alkalosis.³⁷¹ Five of 10 children with salicylate poisoning died from circulatory or respiratory failure.⁷⁸² Fatal salicylate poisoning with hemorrhagic manifestations was reported.^{44, 506, 1814} The doses of salicylates used in rheumatic fever lower the prothrombin content of blood but not seriously; the reduced prothrombin time can be corrected readily by the use of vitamin K.^{269, 546, 1232, 1433, 1593} The use of vitamin C notably improved one patient's tolerance to salicylates.

2. *Treatment of Salicylate Poisoning.* Large quantities of lactate-Ringer's solution and dextrose were given intravenously for several days (Hartmann).⁷⁸² If sodium bicarbonate is given in conjunction with salicylates the concentrations of plasma salicylates may be lowered.^{578, 1432, 1647, 1874}

Sulfonamides. These are of no value during acute rheumatic fever but are apparently of great value in the chemoprophylaxis of the disease as will be discussed later.

Penicillin. The same may be said of penicillin which is of no value during acute rheumatic fever; indeed according to some observers penicillin given at that time aggravates the disease.^{578, 1432, 1828, 1884}

[Penicillin may be useful in controlling certain complications due to hemolytic streptococci; for example, acute otitis media.—Ed.]

Other Drugs. Carditis, toxicity and relapses occurred much less frequently when Gubner and Szucs⁷¹¹ used a succinate compound (calcium double salt of benzoic acid and succinic acid benzol esters) rather than salicylates. To control nervous instability the use of sedatives such as phenobarbital was recommended for children with active and subacute rheumatic fever or chorea (Hubble).

Antireticulocytotoxic Serum (Bogomoletz' A.C.B. Serum). Claims were made by Bogomoletz^{168, 169} and Strazhesko that "rheumatism" was relieved by injecting subcutaneously minute amounts of antireticulocytotoxic serum into patients.

The serum was usually obtained from rabbits immunized against human reticulo-endothelial tissue cells. It is not clear what type or types of "rheumatism" were treated. Bogomoletz^{168, 169} claimed that "in cases of acute arthritis it is a quick and certain cure, but when there is endocarditis, application of the serum has a bad effect." Strazhesko stated: "In chronic rheumatism (chronic arthritis and endocarditis) the serum should not be used."

This serum was investigated for the British Empire Rheumatism Council by Bach.⁴⁸ Among the various rheumatic patients treated were two with rheumatic fever. Results in these cases were negative. The Council did not recommend its use. When informed of Bach's work, Bogomoletz^{168, 169} is said¹⁹⁵¹ to have stated: "The serum is suitable for the cure of rheumatism only in the acute phase of the illness." [Which leaves us as confused as before.—Ed.]

Spinal Fluid "Pumping" (Speransky). Spinal fluid "pumping" in the treatment of rheumatic fever was approved by the Gillmans who espoused the theories of Speransky.⁸⁵³

The rationale and technic were explained thus: Antibodies in the blood stream fail to pass into the nervous system. To cause antibodies to pass across the hematoencephalic barrier into the brain and spinal cord and thus offer protection even against the intrathecal injection of toxins, Speransky developed spinal fluid "pumping"—the repeated withdrawal and introduction of 10 c.c. of cerebrospinal fluid 20 times in 40 minutes. By increasing the permeability of the hematoencephalic barrier, this pumping presumably allowed antibodies (or medicinal agents such as salicylates) to pass into the central nervous system. Pumping also provided "a specific type of nerve irritation" which, under certain circumstances, was said to have remarkable therapeutic value. Pumping, generally in connection with salicylate therapy (for one or two days before and after pumping), was used by the Gillmans⁶⁵³ to treat 100 patients: of 52 "treated during their first acute attack of rheumatic fever," 36 (72 per cent) "recovered completely." Of 33 patients with recurrent attacks 23 (70 per cent) "had no further attacks." Of 127 patients with rheumatic fever treated by salicylates alone (without pumping) only 48 per cent recovered completely. Because the pumping did not produce significant increases in the salicylate content of spinal fluid and because pumping alone was no less effective, the results were presumably not related to salicylates.

Untoward reactions sometimes occurred: severe headache, vomiting, fever. Death from multiple cerebral petechial hemorrhages occurred three days after a second pumping in a hypertensive patient with rheumatic fever; death was considered possibly from hypoprothrombinemia from salicylate poisoning rather than from the pumping. [It was not proved that the supposedly beneficial effects resulted from the pumping rather than from salicylates or from spontaneous remissions which commonly occur. We do not recommend spinal pumping.—Ed.]

Special Treatment for the Heart. To provide a superior form of "cardiac rest" patients with acute rheumatic fever and carditis were treated for long periods in oxygen chambers.¹⁵²⁷ Final results were not given. Edstrom⁶¹⁰ in Sweden reconstructed a hospital ward into a climatic laboratory where the temperature was kept constantly at 32° C. and the relative humidity between 35 and 40 per cent. Of seven rheumatic patients living in this "microclimate," six became free of symptoms and capable of work.

The effects of various drugs on 44 children with congestive heart failure and active rheumatic fever were studied (Walsh and Sprague): Xanthine diuretics were of greatest value. Digitalis was of value but it was necessary to use great care in its administration as three patients who showed toxic effects from digitalis died suddenly. Mercurial diuretics were effective. But if digitalis was given immediately preceding the diuretic, digitalis toxicity could be induced in connection with the loss of fluid.

The problem of cardiac neurosis and the need for adequate mental hygiene was stressed (Ershler⁵³²; Massell and Jones¹¹⁷⁴; Robertson, Schmidt and Feiring; Sieracki).

PREVENTION OF RHEUMATIC FEVER

By Individual Sulfonamide Prophylaxis. The prophylactic use of sulfonamides for the prevention of recurrent rheumatic fever has been studied since 1936 when Thomas and her co-workers, and Coburn and Moore began their work. From 1941 through 1945, 10 different groups of investigators published results of controlled studies.^{24, 309, 332, 173, 549, 752, 753, 1048, 1049, 1051, 1222, 1377, 1734, 1783, 1784, 1785} These studies have been summarized.^{1502, 1630} Small doses of sulfonamides were administered daily to rheumatic patients (not in the active stage of rheumatic

fever) during fall and winter months. Results of treatment and the course of the disease among treated patients were compared with those of an almost equal number of patients who received no sulfonamides. Total results published through 1945 are summarized in table 2.

Among rheumatic patients protected by sulfonamides more than 1,037 seasons only 22 acute exacerbations occurred, an incidence of 2.2 per cent; only three patients died from rheumatic fever. But among rheumatic patients who received no sulfonamides during 1,340 seasons 183 acute attacks (an incidence of 13.7 per cent) and five deaths (to date) from rheumatic fever occurred. In other words, among the patients not protected by sulfonamides there were six times as many acute recurrences and almost twice as many deaths as among those who received sulfonamide prophylaxis.

[In our opinion these results are most impressive and we believe that sulfonamide prophylaxis appears to represent an important medical advance.—Ed.]

Sulfanilamide was generally used: 0.5 to 1 gm. daily for children; 1 to 2 gm. for adults. [Thomas now recommends for adults one daily morning dose of 1 gm.—Ed.] Consensus was that administration should be begun when the active rheumatic attack has subsided, preferably before the patient leaves the hospital so that studies on possible toxicity can be done before the child returns home. Usually the drug was given only during the fall and winter months, or from October to June. But others considered it best to administer it throughout the year.

Toxic reactions were reported variously as "few," "rare, generally mild," "in 10 per cent generally mild." But toxic reactions occurred in more than 30 per cent of the cases of Stowell and Button,¹⁷³⁴ and one death resulted from agranulocytosis in a 12 year old boy who unfortunately neglected to report for appropriate treatment until 60 hours after the onset of symptoms. Most of the toxic reactions, however, consisted of relatively mild rashes, fever, leukopenia, or mild hemolytic anemia which cleared promptly when use of the drug was stopped. The use of sulfadiazine or sulfamerazine may reduce markedly the incidence of toxicity.

Short-time prophylaxis was used by Glazebrook and Thomson⁶⁵⁸ who gave certain school boys with acute tonsillitis 15 to 20 gm. of sulfanilamide for four or five days, none to others. Of 16 cases of acute rheumatic fever which developed later 12 occurred in patients not so treated, only four in those who had received sulfonamide.

By Mass Sulfonamide Prophylaxis. This was first used by the armed services in World War II. Probably more than 1,000,000 men at some time during the war received sulfonamide prophylaxis, generally with sulfadiazine, usually 1 gm. daily. These studies were initiated by the Navy and by the Army Air Forces. The effects of mass prophylaxis on the occurrence of rheumatic fever, meningococcic meningitis, scarlet fever, other hemolytic streptococcic diseases, and respiratory diseases were observed. The incidence of these diseases in a treated group of several thousand persons was compared to that in untreated controls.^{83, 331, 852, 855, 1873, 1943} The incidences of respiratory and streptococcic diseases in the treated groups decreased from 50 to 85 per cent. A reduction in rheumatic fever paralleled that in respiratory diseases (Coburn³³¹; Holbrook⁸⁵⁵). At one station where sulfadiazine prophylaxis was instituted, the rheumatic fever rate fell from 87 to 0 per 1,000 in four weeks (Carter). Similarly complete control of a scarlet fever epidemic and marked reduction in respiratory diseases were reported (Watson, Schwentker, Fetherston and Rothbard).

TABLE II
Summary of Consolidated Reports on Sulfonamide Prophylaxis of Rheumatic Attacks

Investigator	Year	Patients Treated		Untreated Controls		Toxic Reactions
		Person- seasons	Rheumatic Attacks (Definite)	Person- seasons	Rheumatic Attacks (Definite)	
Thomas, France and Reichisman ^{1783, 1784, 1785}	1939 1941 1942 1944	114	4	150	21	Rare, generally mild
Coburn and Moore ³²	1939 1940 1941	184	1	163 100	37 13	In 10%, generally mild
Stowell and Button ¹⁷²¹	1941	46	0	14	2	In more than 30%, one fatal
Hansen, Platon, Dwan and Pennoyer ^{1753, 1777}	1942 1944	131	7	58	27	Rare
Kuttner and Reyersbach ^{1018, 1019, 1051}	1943 1945	108	1	104	23	Had to stop treatment in 15%
Chandler and Taussig ²⁰⁹	1943	41	0	41	5	Few, mild
Dodge, Baldwin and Weber ¹⁷³	1943	170*	6	138	19	Mild and rare
Messeloff and Robbins ¹²²	1943	50	3	60	3	Few, mild
Feldt ¹⁵⁹	1944	89	0	42	3	Infrequent and unimportant
Anderson ²¹	1945	104	0	470	30	Occasional, mild
Total		1,037	22 = 2.2%	1,340	183 = 13.7%	

* Dodge, Baldwin and Weber studied 181 person-seasons but 11 had already been reported by Kuttner and Reyersbach; hence the latter are subtracted for this consolidated report.

[From these and other studies it now seems probable that mass sulfonamide prophylaxis can eliminate meningococcic meningitis, greatly reduce scarlet fever and other streptococcic diseases, and reduce the hospital and dispensary admission rates for respiratory diseases and rheumatic fever, provided only that the bacterial organism is sulfonamide sensitive.—Ed.]

Toxic reactions during this mass sulfonamide prophylaxis were in general mild and infrequent. Among 40,000 persons receiving sulfadiazine studied by Holbrook,⁸⁵⁵ only 0.12 per cent had reactions of any type and only 13 persons (0.03 per cent) lost time from duty. There were no deaths. Coburn³³¹ reported mild reactions (evanescent rashes) in 0.5 per cent of 30,000 troops receiving prophylaxis. More serious reactions occurred about once in each 10,000 cases, incidence of 0.01 per cent. In treating 25,000 persons Lee observed mild reactions in 0.5 per cent, more serious reactions in 0.036 per cent, no deaths.

The problem of sulfonamide-resistant strains of streptococci developing during prophylaxis has not been completely settled. During the individual prophylaxis of the several hundred rheumatic persons over several years no resistant strains developed. The only epidemic in the Army Air Forces caused by sulfonamide-resistant streptococci was introduced to Keesler Field by an inductee from southern California. Sulfonamide prophylaxis had not been used at Keesler Field and so far as the inductee knew he had not received sulfonamide. This Group A, Type 17 streptococcic epidemic did not respond to sulfadiazine prophylactically or therapeutically and produced more than 1,000 cases of streptococcic sore throat, some scarlet fever, and other streptococcic sequelae.^{2, 1251} The Navy had similar experiences with epidemics of sulfonamide-resistant streptococcic diseases. Penicillin was effective in all reported sulfonamide-resistant streptococcic epidemics. The method by which streptococci become resistant is not as yet clear. The work of Demerec suggests that resistance is not induced by the action of the drug on the bacteria but that sulfonamide prophylaxis suppresses or kills off the sensitive organisms, thus "leaving the field" to the occasional sulfonamide-resistant organism.

By Penicillin. The possible use of penicillin for such prophylaxis was mentioned hopefully but no precise data appeared in the literature under review.

By Climate. The marked differences in the incidence of acute rheumatic fever and in the postmortem incidences of rheumatic carditis in various geographic regions has suggested that certain climates may possess considerable prophylactic value. During the war the Army, Navy, and Army Air Forces designated special hospitals located in areas of low incidence to be convalescent centers for several thousand soldiers recovering from rheumatic fever. No final report on recurrences in this group has been published as yet but a preliminary report on the first thousand patients so transferred by the Army Air Forces was made: no recurrences occurred among those remaining in these areas of low incidence (Holbrook and van Ravenswaay⁸⁵⁶). Among 376 other rheumatic patients observed by Miller¹²⁴³ for six months in such a convalescent hospital only two had acute exacerbations while at the hospital; five other patients who had been home on furlough to an area of high incidence returned to the hospital with recurrent attacks.

Initial attacks of rheumatic fever are occasionally seen among natives of regions of low incidence, but *recurrent* attacks are rare among residents or among rheumatic patients coming to the area.^{452, 845, 1602} However, the prophylactic effect of climate can be a solution for very few of the large numbers of rheumatic patients who require protection from recurrences (Boyer).

By Diets and Vitamins. When two boiled eggs and two frozen egg yolks were added by Coburn and Moore³³⁴ to the daily diet of 43 rheumatic children, no recurrences developed even though hemolytic streptococcic infections occurred.

[If this interesting observation can be confirmed it will be most important.—Ed.] "The importance of vitamins A and D, milk, protein, and the value of sun bathing cannot be overemphasized" in the treatment and prevention of rheumatic fever (Peete). Rinehart suggested that vitamin C may have a prophylactic effect against rheumatic attacks. Vitamin C was reported to be specific for nosebleeds occurring in rheumatic fever (Camp and Galvin) and for reducing sensitivity to salicylates so that larger doses may be taken (Pelner).¹³⁶⁰

By Vaccines and Serums. Since 1933 Wasson and Brown^{1877, 1878} have studied the prophylactic effect of streptococcic vaccination. Between September, 1940, and June, 1942, 80 ambulatory children with rheumatic carditis received an average of six intradermal inoculations of tannic acid precipitated toxin of the N.Y.5 strain of hemolytic streptococcus. Only one recurrence was suspected. Of a control group of 62 similar patients 11 had recurrences with three deaths. [These results are impressive but must be confirmed by others before a final opinion thereon can be formed.—Ed.]

By Salicylates. In general salicylates given between attacks have not prevented rheumatic recurrences. But when salicylates were given to rheumatic children at the onset of infections of the upper respiratory tract, some of the (otherwise impending) exacerbations have apparently been prevented (Schlesinger, 1938). Coburn and Moore³³³ administered daily 4 to 6 gm. of sodium salicylate to rheumatic patients as soon as acute pharyngitis started. If throat cultures revealed hemolytic streptococci, salicylates were given for four weeks; otherwise the use of the drug was stopped. Of 47 rheumatic patients having hemolytic streptococcic pharyngitis so treated rheumatic fever developed in only one (2 per cent). Among 139 untreated controls, 57 (41 per cent) had rheumatic fever.

[With this plan salicylates are given at a time when sulfonamides are powerless to prevent recurrences; that is, between the onset of the acute hemolytic streptococcic infection and the usual time for the appearance of the rheumatic attack. If this work can be confirmed, this method may provide a needed supplement to sulfonamide prophylaxis.—Ed.]

By Control of Air-borne Infection. During the war well-controlled studies were made on the effect of oiling floors and bedding in barracks.^{630, 1173} A reduction in respiratory infections resulted. Installation of ultraviolet lights in classrooms, barracks, and hospital wards¹⁵³⁷ also resulted in a reduction of air-borne diseases. Several germicidal vapors (aerosols) gave promising results.^{233, 757, 1117} [These methods of controlling air-borne infections are not yet entirely practical but offer promise for the future when certain technical difficulties can be overcome.—Ed.]

By Community Responsibility and Public Health Services. More than 30 papers recently pointed to the necessity of mobilizing communities against rheumatic fever. Public health measures like those which have been so successful against tuberculosis are needed to control rheumatic fever. The following needs were stressed: adoption of standards for diagnosis and treatment; promotion of facilities for care; coördination and financing of research, and programs of professional and public health education.^{34, 87, 213, 805, 887, 1158, 1191, 1317, 1350, 1463, 1519, 1682, 1918} The United States Children's Bureau recently adopted a program for children with rheumatic carditis.^{501, 865}

[In December, 1943, the American Council on Rheumatic Fever was formed, sponsored by the American Heart Association. Representatives from medical and lay organizations make up its membership. The Council's objectives, briefly, are to foster the extension of

public and private programs for treatment, to secure aid for special studies on rheumatic fever and to promote public and professional education.—Ed.]

SYDENHAM'S CHOREA

Clinical Data. This disease which affects children and young adults, more commonly girls, was considered one of the major manifestations of rheumatic fever (Bennett and Hoekstra). In 25 per cent of rheumatic children chorea is the first sign of rheumatic fever; in another 25 per cent chorea develops some time in the evolution of their rheumatism; some children with chorea never have any (other) rheumatic episode (Hubble).

Chorea is rare in the tropics; one case in a Negro boy from Miami was noted (Saslaw). Electroencephalograms of 23 children with Sydenham's chorea were studied: The tracings were not specific but revealed dysrhythmias like those found in epileptics or in cases of head injuries (Usher and Jasper).

In chorea mitral valvulitis occurs often; aortic valvulitis rarely: six cases of the latter have been reported previously; a seventh was added (Berk).

Treatment. Infectious chorea is a self-limited disease lasting from one to six months, often with recurring attacks. Criteria of effective therapy are (1) whether the duration of the disease has been shortened and (2) whether rheumatic heart disease has been prevented. Artificial fever therapy was considered almost specific. In 17 cases typhoid-paratyphoid vaccine reactions were used to produce temperatures of 104°–106° F. for two hours daily on eight consecutive days (Bennett and Hoekstra). E. L. Bauer⁸⁸ treated 300 patients by such febrile reactions with good results. The presence of acute arthritis, myocarditis or endocarditis did not increase the hazard of treatment. Chorea rarely recurred after a full course of protein shock therapy had been given (Tucker).

Drugs, including salicylates, were of little value. Mental and physical rest and efficient nursing were considered important.¹⁸¹⁸ Three patients were treated successfully with vitamin B₆: chorea may be related to a vitamin deficiency, especially of the B₆ factor (Schwartzman). Several patients were treated with small daily doses of insulin: preliminary results were "remarkably good"; relapses were not noted (Eitzen).⁵¹⁵

ERYTHEMA NODOSUM

Formerly considered a specific disease chiefly if not always related to rheumatic fever, erythema nodosum is now regarded as a nonspecific reaction to a variety of infections or toxic agents, chiefly tuberculous and streptococcic infections,⁵⁸⁸ perhaps less commonly to sulfonamides, coccidioidomycosis and sarcoidosis. In 74 per cent of 27 cases of erythema nodosum among children tuberculin reactions were positive, but among 325 consecutive cases of calcified pulmonary tuberculosis there were only three cases of erythema nodosum.¹¹⁰³ Erythema nodosum affected only 10 of 1,000 patients with acute rheumatism (Perry).

New cases were discussed.^{588, 985, 986, 1103, 1382} Females were affected three times as often as males. A severe type was noted in middle-aged women. The disease appears most often in April and May, rarely in summer and fall. "Erythema nodosum in adults might well be divided into two groups, those with and those without visceral manifestations." Among the 37 cases reported by Kerley

sarcoidosis was exhibited in those in which visceral manifestations were present. Erythema nodosum sarcoidosis in Europe and erythema nodosum coccidioidomycosis ("valley fever"; "valley rheumatism") in California are closely related if not the same disease (Kerley^{985, 986}; Perry¹³⁸²).

CHRONIC ARTHRITIS: THE TWO COMMON TYPES

No nomenclature is acceptable to all, but the English classification designating the two common types as "rheumatoid arthritis" (synonyms: chronic infectious, atrophic, proliferative) and "osteoarthritis" (synonyms: senescent, hypertrophic, degenerative), although neither adequate nor descriptive, is the least confusing.⁹⁶⁹ These terms, adopted by the American Rheumatism Association, are now in common usage in this country.

RHEUMATOID ARTHRITIS

Social and Economic Importance. Because rheumatoid arthritis does not occupy a prominent place in mortality statistics, its importance is woefully underestimated (Eiman). Yet this greatestcrippler of man strikes persons in their most productive years (Margolis). The invalid's burden usually must be shouldered by the family, which more often than not is in poor financial circumstances. Adequate facilities for hospital or institutional care do not exist in any country.¹⁷⁴⁷ In the United States free beds for such patients do not number more than 200, whereas, there are more than 100,000 free beds for tuberculous patients.¹⁰⁷² All in all "the great majority are not well looked after" (Sundelin).

Incidence. Morbidity statistics of the insured population of Scotland would indicate that rheumatoid arthritis is a "relatively infrequent affection" (Halliday⁷¹⁷) in that country. Only 330 cases were reported out of a total of 378,207 instances of incapacity, an incidence of less than 0.1 per cent. This figure may be underestimated as many cases of rheumatoid arthritis probably "were hidden under the vague term of rheumatism." Of about 4,500 "rheumatic patients" seen annually by rheumatologists at the Mayo Clinic, 35 per cent have rheumatoid arthritis (Hench).⁸¹³ [This relative incidence, approximately a third, is found in most large arthritis clinics and prevailed also at the two centers for chronic rheumatic diseases of the United States Army (Hench and Boland).—Ed.] The over-all incidence of rheumatoid arthritis in the armed forces cannot be accurately calculated. Many, but by no means all, gravitated to army general hospitals and many were later sent to special rheumatism centers. Boland and Corr found that 12.4 per cent of 450 consecutive admissions for arthritis and allied conditions at an army general hospital were for peripheral rheumatoid arthritis (peripheral and spinal disease combined were responsible for approximately 20 per cent). For 79 per cent of 105 soldiers with arthritis studied by Wallace at another army general hospital the diagnosis was rheumatoid arthritis. [This incidence appears to be inordinately high and is not comparable to that reported from other army general hospitals. Was such a diagnosis often made for convenience in obtaining hospitalization?—Ed.] The incidence in British military hospitals was less: Savage¹⁵⁴¹ found rheumatoid arthritis in only 1.85 per cent of 270 soldiers admitted for rheumatic diseases (incidence for peripheral and spinal disease combined was 7 per cent). At No. 3 General Hospital (British) rheumatoid arthritis was diagnosed in 6 per cent and fibrositis in 70 per cent of the first 100 cases of rheumatism (Copeman³⁷⁶). Rheumatoid arthritis was a major cause for evacuation of American soldiers from North Africa; such cases outnumbered rheumatic fever, rheumatic heart disease and pul-

monary tuberculosis as non-neuropsychiatric causes for evacuation and were exceeded only by cases of asthma, peptic ulcer and nonulcerous dyspepsia (Short ¹⁸⁹⁹).

That rheumatoid arthritis is a disease of temperate climate was noted again,^{181, 434, 510, 908} but no new data regarding climatic incidence appeared. Cecil ³⁹⁵ remarked that victims of rheumatoid arthritis, "like its first cousin rheumatic fever," predominantly belonged to the poorer classes.

General Clinical Data. Detailed anthropometric studies, comparing body builds of rheumatoid and osteoarthritic patients, were conducted (Seltzer ^{1575, 1576}). Patients with rheumatoid arthritis were not as definitely linear as many clinicians had formerly stressed. The osteoarthritic groups were more distinctive and were highly pyknic showing strong laterality, stocky builds, big bones, big muscles. The average age at the time of onset of rheumatoid arthritis in 388 cases studied by Sclater was 40 years; the onset in 73 per cent of the males and in 66 per cent of the females was between the ages of 25 and 54 years. The ratio of females to males affected was 2.3:1. Kinsella thought that, when the disease began after the age of 50 years, the clinical pattern differed, being characterized by (1) more abrupt onsets, (2) "hot swellings," (3) more stormy and rapidly fluctuating courses, (4) more equal sex distribution, and (5) better prognosis.

In a civilian series initial involvement of fingers was more common in females (38 per cent) than in males (26 per cent) (Sclater). Boland noted that joints of lower extremities were the first affected in 70 per cent of soldiers; metatarsophalangeal and interphalangeal joints of feet were involved in 41 per cent of cases, while the corresponding joints of fingers were affected in only 10 per cent. Such figures suggest that joint trauma plays a part in initial localization (Bach ⁴⁶).

The usual prodromal symptoms and typical clinical pattern were reviewed.^{171, 567, 1004, 1157, 1599, 1968} During the "prearthritic stage" rheumatoid arthritis may easily be confused with such generalized diseases as thyrotoxicosis, psychoneurosis or tuberculosis (Borman; Ropes and Bauer). Typical advanced rheumatoid arthritis, as described in most textbooks, offers little difficulty in diagnosis.^{1493, 1494} But so-called "atypical" cases occur so frequently that it may rightly be questioned whether the clinical pattern of "insidious onset, slow progressive course and symmetrical joint involvement" should be labeled as usual or typical. Examples of atypical onsets and atypical early clinical courses, as observed by Ropes and Bauer, included: (1) asymmetrical involvement, often a monarthritis; (2) sudden febrile onsets precipitated by acute infection and accompanied by skin rash and migratory joint involvement; (3) bouts of arthritis precipitated by respiratory or other infections and not followed by permanent articular residues; (4) febrile onsets resembling rheumatic fever [these were common among soldiers.—Ed.]; (5) transient swellings affecting one joint and then another resembling the "palindromic syndrome"; (6) onset consisting of recurrent joint and muscle aching and stiffness with qualitative characteristics of so-called "primary fibrositis." According to Ropes and Bauer most patients with so-called fibrositis actually have mild rheumatoid arthritis, although often the diagnosis cannot be made until after long periods of observation. Most patients with "chronic synovitis" and "intermittent hydrarthrosis" eventually turn out to have rheumatoid arthritis (Ghornley and Cameron).

Minor roentgenographic deviations in the gastrointestinal tract (ptosis, dilatation and hypotonicity of gall-bladder, stomach, small intestine and colon) were often found in cases of arthritis, including rheumatoid arthritis.^{1366, 1679}

RHEUMATOID ARTHRITIS: SPECIAL CLINICAL FEATURES

Effect of Hepatitis. Complete or partial remissions, though temporary, may result when hepatitis or biliary obstruction of a degree sufficient to produce icterus develops in cases of rheumatoid arthritis. Subsidence of objective manifestations may be striking and demonstrates that the disease is potentially reversible. Two more such instances were noted.^{1164, 1078} Attempts made to imitate this phenomenon experimentally by injecting bile salts and bilirubin intravenously failed.¹⁴ But Gardner, Stewart and MacCallum produced hepatitis by inoculating rheumatoid patients with serum from patients with infective hepatitis. In 32 of 312 rheumatoid patients inoculated jaundice developed. During the incubation period no change in the arthritis was noted, but with the appearance of jaundice dramatic improvement was noted by 18 of the 32 patients (complete remission in 10, considerable improvement in eight). Disappearance of pain and swelling was quickly followed by increase in range of motion. "One patient whose fingers had been locked for two years was able to move them on the third day of jaundice. Then the swelling rapidly subsided, and by the sixth day she had full and painless movement of her fingers." The authors concluded that experimental hepatitis "provides an opportunity of producing a remission under controlled conditions and the possibility of analyzing the mechanism by which it is produced."

How hepatic damage produces its ameliorative effect remains unknown. In (non-jaundiced) patients with rheumatoid arthritis liver function, as gauged by hippuric acid and bromsulfalein tests, is generally normal (Robinson¹⁴⁸⁰). No specific hepatic lesions have been found at necropsy (Rosenberg, Baggenstoss and Hench^{54, 1500}). Snow and Hines studied the effect of obstructive jaundice on experimental arthritis in rats, produced by pleuropneumonia-like organisms. Ligation of the common bile duct prior to, or 20 hours after, inoculation with the organism delayed the onset of arthritis and diminished subsequent degrees of joint involvement. But ligation of the duct after the onset of arthritis did not affect the course of the disease. Arthritis induced by injection of hemolytic streptococci was not influenced by ligation of the bile duct. Snow and Hines suggested that the effect of obstructive jaundice on arthritis produced in rats by pleuropneumonia-like organisms was due to the solubility of these organisms in bile.

Effect of Pregnancy. Not every female with rheumatoid arthritis experiences relief when pregnant but the majority do (Aldred-Brown). A patient refractory to various forms of treatment including gold salts, was relieved completely by pregnancy (Flynn). The arthritis became asymptomatic at the fourth month of gestation, and the remission lasted two and one-half years; reactivation of the disease occurred six weeks after completion of a second pregnancy. In none of Sclater's 388 cases did rheumatoid arthritis first manifest itself during pregnancy. The mechanism of relief in pregnancy, as in hepatitis, remains a mystery.^{583, 1480, 1501} Elevation of serum lipids, total cholesterol and phospholipids is common to both pregnancy and jaundice, but the blood in cases of rheu-

matoid arthritis is not deficient in these fractions.^{101, 165} Because the disease may flare up after the puerperium, pregnancy was considered undesirable (Gill⁶⁵²).

Ocular Lesions. Uveitis was observed in two of 83 rheumatoid patients, and among 63 patients with uveitis, rheumatoid arthritis was noted twice, an incidence of 2.4 and 3.2 per cent respectively¹²⁸; cultural studies from eye washings revealed no constant bacterial or filtrable agent. Two cases of band-shaped opacity of cornea associated with rheumatoid arthritis were reported: one in a 13 year old boy (Wong), another in a four year old girl (Kurnick). Nineteen of 24 additional children who had this rare corneal lesion also had juvenile rheumatoid arthritis. Its pathogenesis, like that of rheumatoid arthritis, is unknown. Smoleroff observed necroscleritis nodosa perforans (scleromalacia perforans, scleritis necroticans) in three patients with rheumatoid arthritis. In two other cases reported,^{27, 557} pathologic changes in scleras consisted of multiple, disseminate and discrete areas of focal necrosis with superimposed subacute inflammatory reaction which developed into relatively large abscesses and finally were reduced to cavities (Fingerman and Andrus).

Cardiac Lesions. Although rheumatic cardiac lesions are found at necropsy in roughly 40 per cent of rheumatoids not nearly that many show evidences of cardiac disease in life, according to previous reports. But Feiring found clinical evidence of "carditis" in eight (29 per cent) of 27 patients with rheumatoid arthritis: "unequivocal auscultatory signs" in two (one had had rheumatic fever), roentgenographic evidence of progressive cardiac enlargement in one, and one or more electrocardiographic abnormalities in five (prolonged P-R interval in two, inverted T wave in two, bundle-branch block in two). Five rheumatoid patients studied by Logue and Hanson exhibited first degree heart block with P-R interval of 0.22 second or more. The disparity between the findings in life and at death indicated that the pathologic lesions are subclinical and not detectable before death (Hench⁸¹⁴).

Amyloidosis. The association of amyloidosis and rheumatoid arthritis rarely occurs,^{704, 1672, 1808} and then only in severe cases of long duration.¹¹⁷⁰ Amyloid degeneration was found at necropsy in two of the 30 cases (7 per cent) of Rosenberg, Baggenstoss and Hench^{54, 1500}; in 13 (21 per cent) of the 61 cases of Fingerman and Andrus.^{27, 557} Fatal amyloidosis of kidneys, spleen and liver affected a rheumatoid patient.¹¹⁷⁰

Palmar Erythema. Palmar erythema may develop in severe or long-standing cases of rheumatoid arthritis and may be relieved by pregnancy or hepatitis (Perera). The peripheral vascular dilatation involves chiefly the eminences of the palms or fingertips, is sometimes called "liver palm," and is found also in other chronic diseases including pulmonary tuberculosis (Trostler), hepatic cirrhosis, and pregnancy (Lofgren). The cause is unknown but an abnormality in the metabolism of 17-ketosteroid hormones has been suggested (Bean^{105, 106, 107}).

PATHOLOGIC CHARACTERISTICS OF RHEUMATOID ARTHRITIS

General. That rheumatoid arthritis is not solely a disease of joints but a systemic disease with widespread pathologic changes in various tissues and organs was emphasized by recent necropsy and biopsy studies. Particular interest was centered on lesions in heart, peripheral nerves and skeletal muscles.

Joints. Bayles⁹⁸ observed at necropsy in 23 cases essentially the same articular changes as the classical ones of Nichols and Richardson (1909), and Allison and

Ghormley (1931). Early changes in subsynovial tissues, as described by Bennett¹²² consisted of diffuse lymphocytic and plasma cell infiltration with the frequent formation of lymphoid follicles. From biopsy studies, Steinberg¹⁷⁰¹ concluded that no specific micropathologic changes exist in rheumatoid arthritis; variable pathologic pictures may be seen ranging "from one in which there is a polymorphonuclear infiltration to sections showing round cell infiltration, both perivascular and nonperivascular." Multiple osteochondral bodies developed in the synovia in one case of "mixed rheumatoid and degenerative arthritis."¹⁸²¹

Studies of joint innervation revealed no nerve fibers in cortical bone or in articular cartilage, but the joint capsule, periosteum and synovial membrane were richly supplied (Smyth and Freyberg^{608, 1050}).

Bones. No new data appeared. Despite marked bone atrophy and cystic degeneration, fractures are infrequent complications of rheumatoid arthritis, and healing following fractures takes place normally (Baer). Large cysts formed above each hip joint in a case of Burt.²⁰⁶

Subcutaneous Nodules. The rheumatoid nodules of four patients consisted of focal fibrinoid degeneration and necrosis surrounded by a palisade-like radiate arrangement of fibroblasts, such as Collins (1937) described previously (Weber^{1890, 1891}).

Peripheral Nerves. Widespread involvement of the peripheral nervous system in rheumatoid arthritis was demonstrated by Freund, Steiner, Leichtentritt and Price.^{601, 602, 603} Lesions consisting of perineural nodules (nodular perineuritis) were irregularly distributed, not only in nerves of extremities but also in peripheral nerves unrelated to joints. The nodules consisted of an outer zone of lymphocytes with scattered plasma cells and an inner zone of polyhedral-shaped cells having large irregular nuclei, "not unlike epithelioid cells seen in other granulomatous tissue." Neuritic pains, paresthesia and trophic changes, common to the disease, might be attributed to such lesions. However, the sensory and muscular degenerative changes of rheumatoid arthritis cannot be entirely explained thereby because the nodules were always perineural, and endoneural lesions which would be expected to produce degeneration were not found.

Muscles. Freund, Steiner, Leichtentritt and Price^{601, 604} also described "nodular polymyositis" (compact microscopic accumulations of lymphocytes, a few plasma cells, occasional epithelioid and eosinophilic cells) in specimens from 15 patients with rheumatoid arthritis. The disseminated nodules, found in biopsies taken at random (gastrocnemius, deltoid, pectoral, rectus abdominis, iliopsoas muscles), were discovered in every case and were considered specific lesions. In 196 control cases no such lesions were found. Associated changes in muscle fibers (irregularly distributed hydropic degeneration, edema, loss of striation, swelling or shrinkage, and atrophy) were found regularly. This degeneration was not related spatially to lesions of the synovia, periarticular structures, subcutaneous nodules or peripheral nerves, but was considered as an independent tissue reaction to the same unknown agent. Such widespread myositis (with coexisting nodular peripheral neuritis) offers an anatomico-pathologic basis for the muscle atrophy of rheumatoid arthritis which heretofore could not be explained on the basis of disuse alone. [These microscopic lesions in muscles notably resemble those in inflamed synovia and subchondral bone in rheumatoid arthritis. One of us, W. B., has found similar lesions in cases of disseminated lupus erythematosus and periarteritis nodosa.—Ed.]

Heart.—The hearts of 152 patients with rheumatoid arthritis were studied at necropsy.^{27, 53, 54, 55, 98, 557, 1500, 1979} In a total of 66 (43 per cent) of these 152 cases, cardiac lesions indistinguishable from those of rheumatic fever were found; the incidence of such lesions varied from 26 to 66 per cent.

In 24 (80 per cent) of 30 cases studied by Rosenberg, Baggenstoss and Hench^{54, 55, 1500} cardiac lesions were found. The lesions were "rheumatic" in 16 (53 per cent), "nonrheumatic" in eight (27 per cent) of the 30 cases. The rheumatic heart disease was the cause of death in seven of the 16 cases, although in none of these was there a history of rheumatic fever. Gross lesions were present in the mitral valve in 10, in the aortic valve in six, in the tricuspid valve in two, in the pericardium in six. These changes were subacute in three, chronic in eight, and inactive in five. Aschoff bodies were found in valves, pericardium or myocardium in all but two cases. Although pathologically identical, the lesions were considered less severe and less widespread than those seen in rheumatic fever.⁵⁵

Rheumatic cardiac lesions were found by Bayles at necropsy in six (26 per cent) of 23 cases. In only one case was there a history of rheumatic fever; omitting this case, five of 22 (23 per cent) patients dying with rheumatoid arthritis had rheumatic cardiac changes at necropsy unexplained by a known previous attack of rheumatic fever. Similar rheumatic cardiac lesions were found by Fingerman and Andrus^{27, 557} in 19 (31 per cent) of 61 cases of rheumatoid arthritis, in only two of which there was a history of rheumatic fever. Young and Schwedel found at necropsy cardiac lesions in 33 (87 per cent) of 38 cases of rheumatoid arthritis: the lesions were "rheumatic" in 25 (66 per cent), "nonspecific" in 8 (21 per cent) of the 38 cases. A history of rheumatic fever was noted in only three cases, of probable rheumatic fever in two others.

Various explanations were offered for these findings: (1) that rheumatoid arthritis and rheumatic fever are closely related, possibly identical diseases; (2) that the lesions found represented not "rheumatic carditis" (of rheumatic fever) but "rheumatoid carditis," which idea would necessitate a complete revision of thought about the supposed specificity of the lesions of rheumatic carditis; (3) that the patients actually had had two diseases, rheumatoid arthritis and rheumatic fever, the latter generally having been insidious and unsuspected in life because of the general absence of acute rheumatic polyarthritis.⁸¹⁴ None of these explanations are entirely satisfactory; certainly these incidences of rheumatic cardiac lesions among rheumatoids are much greater than those heretofore reported in ordinary necropsy studies on the general population. But according to Hall and Anderson the incidence of rheumatic stigmata in hearts studied at necropsy is much higher than has been supposed and such stigmata were found in 112 (about 90 per cent) of 124 hearts which by ordinary criteria would have been considered "nonrheumatic" (free of gross valvular lesions; no clinical evidence of rheumatic infection or valvular disease in life). Minimal thickening of mitral valve leaflets was observed 74 times (66 per cent) and the chordae of the mitral valve were thickened in 42 cases (37.5 per cent). Characteristic stigmata (arteritis, fibrinoid change, elastic tissue alterations, Aschoff bodies, infiltration histiocytes) were abundantly present. Aschoff bodies were found in 33 cases (29.5 per cent) and "Aschoff-like collections" in an additional 34 (30 per cent). This suggests that minimal subclinical cardiac lesions of rheumatic fever are widespread throughout the general population. [Most of these lesions were microscopic; most of those in the rheumatoid patients were associated with gross changes.—Ed.]

Other Organs. Baggenstoss, Rosenberg and Hench^{54, 1500} were unable to demonstrate lesions pathognomonic of rheumatoid arthritis in other visceral organs. Fibrous adhesions between visceral and parietal pleura were present in 22 of 30 cases, but no relationship between the healed pleuritis and rheumatoid arthritis was established. In

a high (63) percentage of their 30 cases evidence of glomerular endothelial proliferation was present; perhaps the agent responsible for rheumatoid arthritis is also responsible for a low-grade, essentially subclinical glomerulitis. Moderate hypertrophy of lymph nodes, due to nonspecific hyperplasia of endothelial cells both within sinuses and within follicles, was found in eight cases. Coincidental lesions, apparently unrelated to rheumatoid arthritis, in gall-bladder, liver, gastrointestinal tract, spleen, pancreas, adrenals, thyroid, prostate and blood vessels occurred with about the same frequency as in routine necropsy cases.

Causes of Death. Three postmortem series included data thereon.^{98, 557, 1500} Pulmonary complications, not related directly to rheumatoid arthritis, led the lists: miscellaneous pulmonary conditions (pulmonary embolism, bronchiectasis, bronchopneumonia, fat embolism, postoperative atelectasis and so on) were causes in 11 of 30 cases studied by Rosenberg, Baggenstoss and Hench¹⁵⁰⁰ and in five of Bayles' 23 cases. Cardiac causes were second in frequency; in nine (30 per cent) of Rosenberg, Baggenstoss and Hench's¹⁵⁰⁰ cases (rheumatic heart disease in seven, nonrheumatic coronary thrombosis in one, myocardial degeneration with decompensation of unknown cause in one); in four (17 per cent) of Bayles' cases (bacterial endocarditis in three, aortic stenosis with failure in one). Renal lesions caused death in three cases of each series. The remaining patients died of miscellaneous causes. The causes of death in the 61 cases of Fingerman and Andrus were: bronchopneumonia in 24, septicemia and pyemia in nine, lobar pneumonia in eight, tuberculosis in seven, carcinoma in three, amyloid disease in three, cardiac decompensation in three and uremia in two. [Not stated in two cases.—Ed.]

LABORATORY DATA IN RHEUMATOID ARTHRITIS

Roentgenograms. The usual abnormalities were reviewed.^{1022, 1754, 1905} Roentgenographic alterations often are absent in early cases¹⁵⁰⁹: only 25 per cent of Short's patients,¹⁵⁰⁹ observed in an overseas general hospital, demonstrated roentgenographic changes; these usually were of varying degrees of bony atrophy. A common mistake is to rule out rheumatoid arthritis if roentgenograms are negative (Comroe³⁰⁴). Many different forms of arthritis exhibit the same basic alterations. Camp recognized the limitations of the roentgenologist in differentiating between the various types.

"If there is osteoporosis of the epiphyses and beginning narrowing of the cartilage space but no other abnormality of bony contour, the roentgenologist may recognize the changes as those of atrophic arthritis. There is probably some periarticular swelling. If there is a little marginal lipping of bone, instead of calling it atrophic and hypertrophic arthritis, he may discount the lipping and still call it atrophic arthritis. If there is considerable lipping with atrophy of bone and loss of cartilage space, what should he call it? Atrophic and hypertrophic arthritis? Clinically the patient should not have both, but roentgenologically he often has both. For example, an obese man with chronic atrophic (rheumatoid) arthritis will often have typical atrophic changes in the hand and ankle, but in the ankle he will also have considerable proliferation of bone. The roentgenologist cannot differentiate the atrophic changes seen in some cases of mild but moderately advanced gonorrheal arthritis from atrophic (rheumatoid) arthritis. If one has traumatic periartthritis (stiff, painful shoulder from injury, yet no alteration in cartilage or bone), it is not 'arthritis,' but if the arm is immobilized long enough in a sling or at his side the roentgenogram will reveal

osteoporosis in the shoulder joint. How can this be differentiated from early atrophic (rheumatoid) arthritis? In short many conditions may produce the same roentgenographic manifestations. The pathologic and roentgenographic response of joints in various diseases is too similar to permit dogmatic interpretation of the roentgenogram" (Camp).

Blood Counts and Plasma Proteins. Seventy-four per cent of 100 patients with rheumatoid arthritis had hemoglobin values of less than 80 per cent, presumably due to "toxemia" (Haden⁷²⁷), but Robinson¹⁴⁸⁰ concluded that the anemia is partially due to simple plasma dilution similar to that which occurs in pregnancy. Plasma protein values were consistently elevated in cases of severe rheumatoid arthritis (average of 4.11 gm. per kilogram of body weight versus a normal of 2.73 gm.), and the red cell volume was consistently reduced (29 mg. per kilogram of body weight versus a normal value of 34 mg.). The rise in plasma protein was thought to produce a hydremic effect and relative anemia from plasma dilution. The leukocyte picture is not characteristic⁷²⁷; leukopenia is frequent but occasionally mild polymorphonuclear leukocytosis occurs¹⁵⁹⁹; the differential count is rarely altered and toxic granulation is not observed.⁷²⁷

Sedimentation Rate of Erythrocytes. Generally accepted¹⁷²⁵ as a useful index of the disease's activity, this test was considered by some as inaccurate.^{1599, 1661, 1706} In 50 per cent of Short's¹⁵⁹⁹ early or mild cases rates were normal. Steinberg and Loewenstein observed patients with "hot swollen joints" whose rates were normal and patients with clinically inactive disease whose rates were increased. Some¹⁶⁶¹ stated that careful clinical evaluation was much more dependable than the sedimentation rate both in diagnosis and in following the course of the disease. Fibrinogen and euglobulin contents of plasma tend to decrease as clinical improvement occurs, but the decrease in sedimentation rate and plasma proteins is not simultaneous.¹⁷⁵⁷ Usually fibrinogen returns to normal more slowly; the lag is interpreted as indicating continued activity despite a normal sedimentation rate.

Miscellaneous Tests. Retention of Congo red is not always diagnostic of amyloidosis; a rheumatoid patient retained 50 per cent of the dye (normal loss 20 to 30 per cent): amyloidosis was suspected but not found after death from hepatic cirrhosis.¹¹⁶⁴ The Weltman reaction (coagulation of serum proteins in the presence of the electrolyte CaCl_2), was considered a sensitive indicator of activity in rheumatoid arthritis (Milles and Salt). In severe disease a shift to the left was usually found, and a shift to the right was thought to be a sign of good prognosis. But others¹⁷⁰⁶ considered that the test did not reflect the severity of the clinical picture, and Kling considered that the sedimentation rate of erythrocytes was a more accurate guide.

Liver function as measured by the hippuric acid test was subnormal in seven of 13 patients, a deficiency no greater than that found in "any other group of patients suffering from systemic disease." The test was not appreciably affected by gold therapy.⁸²³ Amounts of acetylcholine esterase in blood serum of patients with "arthritis" (type not stated) were normal.²⁶⁸ [They are low in pregnancy and severe hepatic damage, an interesting point in relation to the effect of pregnancy and hepatitis with jaundice on rheumatoid arthritis.—Ed.]

Mester¹²²³ described a test said to have special sensitivity for rheumatic patients. A leukocyte count is made, then an aqueous solution of salicylic acid is injected intradermally, and 30 minutes later another leukocyte count is made. According to Mester¹²²³ 98 per cent of rheumatic patients with acute, subacute or chronic disease but no controls showed a drop in the leukocyte count 30 minutes after the injection. However, Copeman and Stewart found the test to be of no aid in differentiating rheumatic from nonrheumatic diseases and warned against making a diagnosis based on its results; results were frequently negative in cases of frank rheumatic disease and

positive in a number of nonrheumatic conditions. Mester's test, employed by Green and Freyberg⁶⁸⁶ in 20 cases of rheumatoid arthritis gave positive results in only five; they considered it grossly unreliable.

Films of small amounts (1 c.c.) of blood plasma on the surface of water were studied in cases of rheumatic disorders (Scull and Pemberton). The size of the film normally is about 550 sq. cm. and presumably is related to the concentration of plasma proteins. In cases of severe rheumatoid arthritis the films were found to be smaller (150 to 450 sq. cm.) than normal. Indoluria which does not occur in normal persons under normal conditions, was present consistently in patients with rheumatoid arthritis (Neuwirth¹²⁹³). The mean plasma fibrinogen fraction was elevated in 53 cases of rheumatoid arthritis (mean of 520 mg. per 100 ml. of plasma versus a normal of 250 to 400 mg. per 100 ml.). Mester considered fibrinogen estimations to be of diagnostic aid.

Various tests on cerebrospinal fluid were made by Ludwig, Short and Bauer on 101 patients with rheumatoid arthritis. Fifty-nine had rheumatoid arthritis of peripheral joints and 42 had spondylitis with or without involvement of peripheral joints. Determined were the spinal fluid pressure, cell count, values for sugar, chlorides and protein, and the colloidal gold curves. The only significant abnormalities noted were increased concentrations of protein, abnormal colloidal gold reactions, or both. Concentrations of protein were increased (46 to 70 mg. per cent) in 6.8 per cent of the 59 patients with only peripheral joint involvement, in 28.6 per cent (47 to 105 mg. per cent) of the 42 with rheumatoid spondylitis, in 15.8 per cent of the total 101 patients. Colloidal gold reactions were abnormal in five (8.5 per cent) of the patients with peripheral joint involvement and in six (14.3 per cent) of those with spondylitis. These various abnormalities were considered to be the result of alterations in serum proteins and of an increased permeability of meninges caused by their proximity to inflamed articular tissue.

ETIOLOGY AND PATHOGENESIS OF RHEUMATOID ARTHRITIS

Factor of Infection. 1. General Comment. There is no proof that rheumatoid arthritis is an infective disease. Carefully conducted cultivations of blood and joint fluid have produced negative results. But many features suggest that infections play some part (Davidson⁴³⁴). These include: (1) clinical features of fatigue, weight loss, low-grade fever, lymphadenitis; (2) elevated sedimentation rate of erythrocytes and leukocyte counts; (3) frequent elevations in streptococcic agglutination and antistreptolysin titers; (4) frequent positive skin tests for streptococcic protein fractions. But, as Davidson pointed out, fever, leukocytosis, elevated sedimentation rate and other signs are not pathognomonic of infection; they occur in various diseases accepted as noninfectious, including gout (acute gouty arthritis). The finding of agglutinins, antistreptolysins and positive skin tests means only that the patient has been infected with streptococci, not that the arthritis is due to this organism.

2. Foci. "Infected focus" and "focal infection" are not synonymous terms (Shuster). An infected focus is a circumscribed region of tissue infected with pathologic organisms, whereas focal infection implies metastasis, from the infected foci, of bacteria or their toxins, capable of injuring contiguous or distant tissues. The mere presence of pathogenic bacteria in a focus does not necessarily imply the development of systemic infection.

The points for and against septic foci being of etiologic importance were summarized (Davidson⁴³⁴); those for this idea included the following: (1) streptococcic

infections of throat, tonsils or nasal sinuses may precede the initial or recurrent attacks; (2) dramatic improvement sometimes follows removal of a septic focus; (3) the pathologic and anatomic features of lymphoid tissue in tonsillar infection, sinus infection and root abscess suggest that toxic products can be absorbed into the circulation; (4) a temporary bacteremia may occur immediately after tonsillectomy or tooth extraction and after vigorous massage of the gums. Points against the idea included: (1) often no infected focus can be found; (2) usually when a focus has been extirpated, no dramatic results are produced; (3) many persons in perfect health or suffering from diseases other than rheumatoid arthritis may have septic foci in the same situations and of the same magnitude as patients suffering from rheumatoid arthritis.

In a study of 388 cases of rheumatoid arthritis Sclater obtained a history of some type of infection occurring within two months of the onset in 12 per cent of the males and in 21 per cent of the females; infected foci were present in 38 per cent. Pemberton¹³⁷⁰ stated that infected foci should be considered as one of the "drags" of the disease, not as a cause. But others^{49, 1004} considered foci often to be chief etiologic factors.

In one series of 343 patients with rheumatoid arthritis, 57 per cent had infected foci somewhere¹⁰⁷¹; among 55 other patients, 65 per cent had some dental infection; 29 per cent had periapical infection.¹³⁰³ Perhaps dental infections are the result rather than the cause, the periodontal tissues participating in the general lowered resistance. Neither hypercementosis nor pulp stones were thought to be related to arthritis,¹⁰⁷⁶ but severe periodontoclasia was considered a common focus.⁶²⁷ Teeth showing periapical rarefaction in roentgenograms are considered infected and should be extracted^{527, 690}; pulpless teeth without periapical rarefaction should be considered as questionable, not condemned, and roentgenograms made of them at intervals. But Goldberg⁶⁶¹ warned that cultures prove that roentgenograms are frequently unreliable in demonstrating root infection. Exercising rigid precautions in technic and culturing extracted apices of teeth in brain broth and soft brain-agar media, Stein¹⁰⁹⁹ obtained positive cultures from 15 per cent with living pulps (indicating a probable percentage of error in other figures), from 74 per cent of pulpless teeth with periapical radiolucent areas, from 71 per cent of pulpless teeth without periapical rarefaction.

The disease was ushered in by upper respiratory infections in 20 per cent of the cases of Boots and McCollen. Sclater found tonsils the most commonly infected focus; they were infected three times as often as teeth, 7.5 times as often as sinuses, about nine times as often as genitourinary tract and almost 100 times as often as gall-bladder. Evidence of chronic infection of viscera was disclosed in seven of Baggenstoss and Rosenberg's 30 cases (chronic cholecystitis in two; "moderate" chronic interstitial pancreatitis in three; chronic suppurative prostatitis in two). Bach⁴⁹ alone incriminated the colon and still spoke of it as a "focus of toxemia."

Green and Freyberg⁶⁹⁵ studied the incidence of brucellosis in 25 cases of rheumatoid arthritis. Using agglutination tests, skin tests and phagocytic indexes as diagnostic criteria, no evidence of brucellosis was found in any case.

3. *Cultures of Blood and Joints.* Fraser⁵⁹⁰ cultured in beef-heart infusion broth the blood of 61 patients with rheumatoid arthritis: no organisms were recovered in 58 (after 30 days' incubation); in three diphtheroid bacilli were isolated. Streptococci were never recovered. From five of 61 controls positive cultures were obtained: *Streptococcus viridans* in three, diphtheroid bacillus in two. Angevine, Rothbard and Cecil could find no significant organisms in blood, joint fluid, synovia or subcutaneous nodules. Pleuro-pneumonia-like organisms were cultured from prostatic secretion, urethra, cervix or vagina of seven patients with rheumatic complaints; two had rheumatoid arthritis (synovial fluid culture was made in one and found sterile), one had

"polyarticular swelling," and four had articular or muscular symptoms (Dienes and Smith ⁴⁶⁸). That the joints and related involved structures remain sites of secondary metastatic foci after original septic foci have been removed was again suggested.⁹⁸³

4. *Precipitins*. No new data appeared.

5. *Agglutinins*. Patients with rheumatoid arthritis had agglutination titers of 1:160 or higher for hemolytic streptococci more often (58 per cent) than did normal controls (14 per cent) or patients with osteoarthritis (28 per cent) (Ferry and Hunt). The percentage of elevated titers for *Streptococcus viridans* was the same (20 per cent) in cases of rheumatoid and of osteoarthritis. The conclusion drawn was that elevated titers did not prove, but suggested, that hemolytic streptococci are etiologically related to rheumatoid arthritis.

6. *Antistreptolysins and Antifibrinolysins*. Increased titers for serum antistreptolysins are not characteristic of rheumatoid arthritis but in rheumatic fever they are usually present (Short and Bauer ¹⁰⁰¹). Perry ¹³⁸¹ found increases in streptococcic antifibrinolysin titers in only two of 33 patients with peripheral rheumatoid arthritis and in one of eight patients with rheumatoid spondylitis. Bactericidal properties for hemolytic streptococci were detected more often in synovial fluids in cases of rheumatoid arthritis (two of nine cases) than of other articular disease (two of 28 cases) (DeGara).

Theory of Bacterial Allergy. Several favored this theory.^{434, 602, 1302, 1501} Sclater wrote: "If infection is important it is probably not the frequency or the severity of the infection that is significant but perhaps the abnormal response of the patient to infection." Goldberg ⁶⁶² considered such pathologic changes as perivascular lymphocytic and plasma cell infiltration in synovial villi suggestive of an allergic reaction. Davidson's concept ⁴³⁴ was that patients with rheumatoid arthritis have an abnormal immunologic response, the tissues being sensitive to bacterial antigens. Whereas, "the normal response to infection is the development of immunity, an abnormal response produces a state of allergy." He pictured bacterial antigens entering the circulation, coming in contact with fixed tissues in joints and provoking an allergic reaction "evidenced by an explosive discharge of histamine-like substance which produces dilation and increased permeability of capillaries," and hence, "swelling of soft tissues, heat and pain."

Virus Theory. No new data appeared.

Factor of Trauma. Although not the direct cause, trauma may at times act as the agent which precipitates the onset (Ryden). By lowering local resistance, major or minor injury to joints strongly influences the location of arthritic involvement (Kelchner; Lewis ¹⁰⁰⁴).

Factor of Circulatory Disturbance. The peripheral vascular responses of patients with rheumatoid arthritis follow a characteristic pattern, according to Naide, Sayen and Coniroe.

The basal vascular tone was high and peripheral vessels were easily constricted (i.e., vasospastic type). This pattern was thought to account for the thin atrophic skin with cold clammy hands and feet, cutaneous pigmentation, causalgia, hyperesthesia, symptomatic improvement from vasodilating procedures and perhaps flare-ups of the disease after emotional upsets and exposure to cold. Rheumatoid arthritics were found to have been of the vasospastic type before the disease actually developed. Normally high vascular tone is more common in women than men and is most marked in fingers and toes; this may account for the sex incidence affecting females and the predilection for involvement of finger and toe joints. Steinbrocker and Samuels made oscillometric readings in 47 cases of rheumatoid arthritis: in 60 per cent vasospastic arterial disturbances were noted. Only 33 per cent of 71 patients with osteoarthritis showed similar findings. Entirely different results, however, were reported by Benatt and Taylor who, taking skin temperatures of finger tips and recording the response

to immersions in hot and cold water, found that patients with rheumatoid arthritis had normal responses; no specific type of functional vascular reaction could be detected. No evidence of increased vascular tone was elicited.

Factor of Altered Metabolism. Standard glucose tolerance tests, with simultaneous determinations of sugar in arterial and venous blood, were done in eight cases of rheumatoid arthritis.²⁰ Diminished tolerances for carbohydrates were found in all, which to Andrews and Muether indicated decrease in the glycogenic function of the liver rather than pancreatic dysfunction or circulatory stasis. Block and Murrell found no abnormalities in total sulfur, total nitrogen and amino acid contents or total serum proteins in rheumatoid arthritis. According to them, such negative findings invalidated any suggestions that an altered composition of total serum proteins in arthritic patients reflects disturbed sulfur metabolism. Total lipid, total cholesterol and phospholipid contents of the plasma were normal.^{101, 155} Calcium and phosphorus metabolism studies were made in nine patients^{149b}: in seven (78 per cent) the excretion of calcium in urine and feces was greater than normal, but phosphorus metabolism was essentially normal in all. The negative calcium balance was slight but definite (average excretion of 15.1 mg. per kilogram of body weight versus average normal excretion of 12.7 mg.) and was considered indicative of an increased rate of calcium metabolism. A definite correlation existed between the amount of decalcification noted roentgenographically and the rate of calcium excretion. Six of the nine patients with osseous atrophy had negative calcium balances averaging 0.61 gm. per day; three patients without atrophy had negative balances averaging 0.30 gm. One author¹⁵⁰⁷ vaguely discussed "multiple metabolic deviations" that supposedly characterize the "rheumatoid state."

Factor of Diet. Detailed analyses of diets used by 31 patients for a year before the onset of rheumatoid arthritis were made (Bayles, Richardson and Hall). The "pre-rheumatic" intake of calories, protein, fat, carbohydrates, vitamin A and its precursors, thiamine, riboflavin, vitamin C, calcium and iron was essentially the same as for nonarthritic persons living in North Atlantic states. Conclusion: "If a food deficiency contributes to the onset of rheumatoid arthritis, it must be caused by an increased total requirement rather than a deficiency in diet." One author¹⁸²² considered allergy to various foods an important causal factor in arthritis. [No satisfactory supporting evidence was given.—Ed.]

Factor of Vitamin Deficiency. Lowered values for carotene pigments, carotene and xanthophyll as well as vitamin A itself have been reported previously in cases of rheumatoid arthritis (Race, 1937; Eilman, 1939) but no new data appeared. Mild states of vitamin B deficiency, manifested by mild dermatitis, sore mouth and red tongue, are seen at times when the disease is accompanied by marked anorexia and malnutrition (Freyberg⁶⁰⁵), but such deficiencies should be considered as complications, not causes of the disease. No striking differences were found in the riboflavin values of eight normal persons and of 56 patients with rheumatoid arthritis (Bradford and Coke). Most patients (62 per cent) with rheumatoid arthritis have abnormally low values for plasma ascorbic acid⁶⁰⁵ but clinical scurvy is rare. Freyberg⁶⁰⁵ found no relationship between the severity of the arthritis and the ascorbic acid content of blood, and although treatment with vitamin C corrected the deficiency, the course of the arthritis was unaffected. But Bradford¹⁹⁸ considered that some correlation existed between low vitamin C levels and excessive tiredness, tendency to bruising and gastric disturbances in patients with "rheumatic diseases."

Factor of "Intestinal Toxicosis." This almost forgotten theory still has disciples,^{84, 600, 828}

Factor of Endocrine Abnormality. Although a few believe otherwise,^{1138, 1282, 1372, 1732} there is no conclusive evidence that endocrine imbalance plays a part in the production of rheumatoid arthritis^{1094, 1601}; the simultaneous occurrence of some form

of endocrine dysfunction is no more frequent than can be explained by chance (Davidson¹³⁴). But Pemberton and Scull¹³⁷² believed that both rheumatoid and osteoarthritis may be related to disturbances "of the neuroendocrine system as a whole and especially those of the pituitary gland." Selater correlated the time of onset of rheumatoid arthritis with the cessation of menstruation in 132 females; in 19 (14 per cent) the disease began during menopause (a time latitude of two years before and two years following cessation of menstruation was allowed). This was considered a chance association; the conclusion was drawn that "menopause does not tend to precipitate the onset of rheumatoid arthritis." Low basal metabolic rates were found to be the rule in patients with any low-grade chronic disease. In 166 debilitated persons, including patients with "chronic arthritis," the mean metabolic rate was -8 per cent (Stiles¹⁷²⁶).

Psychogenic Factor. The accelerated interest in psychosomatic medicine has extended to the field of rheumatic diseases. Opinions vary, however, as to what part psychogenic factors play in the etiology, predisposition, precipitation, and clinical course of rheumatoid arthritis. Some current views are: "Without implying that rheumatoid arthritis is of psychogenic origin, we do believe that the physician must recognize the fact that worry, grief and anxiety can be major contributory factors of this chronic disease" (Short and Bauer¹⁰⁰¹). "I am prepared to believe that an emotional crisis may predispose or precipitate arthritis in a patient whose body contains the fundamental bacterial or other causative agent of the disease, but I do not believe that without the latter the disease can be produced by psychic distress alone" (Hench⁸¹³). "We hold no brief for the concept that organic joint disease, such as chronic rheumatoid arthritis, may be caused by psychic conflicts, *per se*" (Boland and Corr). "There is no evidence for a primary psychogenic cause; psychological elements are of importance not as causes of rheumatism but rather as sequels to it, often remaining latent until activated by a rheumatic attack" (Medical Advisory Committee on Chronic Rheumatic Diseases for Scotland¹²¹⁵). But Cecil^{301, 306} stated that psychic factors were more important than infection in provoking the original symptoms or in bringing about relapses of rheumatoid arthritis.

Emotional factors were studied in 25 cases by Patterson, Craig, Waggoner and Freyberg and by Martin.¹¹⁶¹ About half of the group experienced prolonged emotional stress (for periods of months) preceding the onset of rheumatoid arthritis. Discussion of their emotional problems caused a fall in skin temperature indicating a change in peripheral circulation. The importance of this mechanism in the development of arthritis could not be evaluated conclusively; its influence appeared to be greater in producing exacerbations of the disease.

Halliday⁷⁴⁴ discovered a "definite upsetting event" antecedent to the onset in nine of 20 cases of rheumatoid arthritis, and in seven cases emotional conflicts were thought to have provoked recurrences. The emotional disturbances included shock following acute danger (air raids, assaults and so on), anxiety over finances or the misbehavior of relatives, fear of loss of an object, paranoid resentment concerning superiors, frustration at being jilted and others. The patients were described as having a restriction of feeling and of emotional expression "so characteristic of rheumatoid patients." He pictured patients with rheumatoid arthritis as "a quiet decent lot," with "relative poverty of facial expression," "who habitually hide and repress many aspects of their inner emotional life." Their manner is that of "quiet friendliness," and they do not "fidget or squirm or show obvious nervous movements"; after the onset of their illness the majority have a "cheery" attitude which produces the

effect of "truly touching patience." To Halliday⁷⁴⁷ such behavior and moods bespeak self-limitation and restriction of feelings and emotions. He considered that this restriction began in childhood; as children they were shy and retiring; in later life they tended to lead a quiet life, were essentially "home birds" and had obsessional trends, being "markedly orderly, punctual, tidy and overly clean." Of 14 females, eight professed to be either frigid or disinterested in sex; of six males, three were "markedly fixed to their mother or sisters." Halliday⁷⁴⁷ summed up the "rheumatoid personality" as a "self-limiting, emotionally inhibited, rather independent (but passively so) type of personality" which not infrequently "is associated with various psychosomatic disorders." During the long period of nightly bombings of Britain, the number of cases at rheumatic clinics increased (Savage¹⁵⁴⁰). But most of the rheumatoid arthritics (even the complete cripples) displayed stoicism while the "fibrositics" demonstrated the greatest emotional reaction (Aldred-Brown).

Other Etiologic Factors. Waine, Bauer and Bennett wondered if some causative factor might be circulating in the blood which would be excreted by kidneys and which could be recovered in urine. They injected unprocessed urine from patients with active rheumatoid arthritis, also alcohol and chloroform extracts of urine into 12 rats, but joint lesions did not develop. Freund⁶⁰⁰ observed that whereas normal urine digests nucleoprotein from normal joint fluid, urine from rheumatic patients left the added nucleoprotein completely unchanged; the significance was not explained. Changes in water balance were found to affect articular symptoms (Jacobsen and Lichtentritt and Lyons). The adding of ammonium chloride (6 gm. daily) to a fixed diet which thereby produced loss of water resulted in decrease in pain, joint swelling and increase in mobility. The changes were reversed when sodium bicarbonate (6 gm. daily) was added to the diet.

General Conclusions on Etiology. In a word, we are still in the dark as to the cause of rheumatoid arthritis¹⁰⁹⁴ despite the enormous amount of research carried on during the past years.

RELATIONSHIP BETWEEN RHEUMATOID ARTHRITIS AND OTHER DISEASES

Rheumatic Fever. The frequent finding of rheumatic carditis at necropsy in cases of rheumatoid arthritis coupled with the not infrequently observed clinical transition of *apparent* rheumatic fever into chronic rheumatoid arthritis has convinced some observers^{53, 54, 98} that the two conditions are closely related, if not the same disease with different predominant manifestations. [See data under "Relationship of Rheumatic Fever to Other Diseases" and under "Pathologic Characteristics of Rheumatoid Arthritis: Heart."—Ed.] Collins³⁵⁹ suggested that rheumatoid arthritis may be a "lente" form of rheumatic fever, and Young and Schwedel stated that there was no fundamental purpose in separating the two diseases. Feiring wrote: "Clinical studies and pathologic findings lend support to the growing conviction that sharp and recognizable differences do not exist between the two diseases. Because the symptomatology overlaps, because the same anatomic elements of the organism are affected, and the same morbid phenomena are expressed, the association appears to be more than simply fortuitous. In fact, the striking and identical features common to both diseases prompt serious consideration of Charcot's premise that, fundamentally, both diseases are different clinical reflections of the same diathesis." Bohan's¹⁷⁰ view was similar. But Hench⁸¹⁴ thought that the two diseases must be carefully distinguished. He maintained that the finding of rheumatic heart lesions in patients with rheumatoid arthritis probably represented "the presence of two coincidental diseases."

[One of us, P.S.H., as an army consultant on rheumatic diseases in the recent war, saw many soldiers whose *presumed* rheumatic fever had slowly progressed into chronic rheumatoid arthritis. But examination in many such cases and of many records failed to reveal a single case in which undoubted rheumatic fever progressed into, or precipitated, undoubted rheumatoid arthritis. In most of the cases the condition was simply acute or subacute febrile rheumatoid arthritis, which in a few weeks became relatively afebrile chronic rheumatoid arthritis. Even in the early "rheumatic fever-like phase" of this acute febrile rheumatoid arthritis much confusion would have been avoided had sufficient attention been paid to the following: the *progressive* (rather than migratory) nature of polyarticular invasion; the general absence of prodromal pharyngitis (although in some cases a confusing pharyngitis occurred after the onset of the arthritis); the slower rises and more moderate elevations of sedimentation rates (rather than the rapid and marked rises characteristic of acute rheumatic fever); the poor effect of salicylates and sometimes the relatively early appearance of roentgenographic changes in joints even in the "rheumatic-fever phase."—Ed.]

Still's Disease. This will be discussed in the section on "Still's Disease and Felty's Syndrome."

Gonorrhea. Like certain other acute infections (influenza, acute respiratory infections) acute genital gonorrhea can precipitate, reactivate or notably aggravate rheumatoid arthritis. Under such circumstances the latter is often mistaken for "gonorrheal arthritis (supposedly) resistant to chemotherapy and fever therapy" (Hench and Boland).

TREATMENT OF RHEUMATOID ARTHRITIS

General Remarks. The multiplicity of recommended treatments indicates that no prompt cure is available (Ensign). Most patients do not demand to be cured. They are grateful for small favors and usually are happy if they get some relief (Hench⁸¹³). An optimistic, courageous attitude is required of a physician who does not wish to see some of his patients wander off to patent remedies and quacks. "He must even compromise at times with his intellectual honesty and employ methods of doubtful value to hold the patient to the pursuit of a few simple measures of proved value" (Short and Bauer¹⁶⁰¹).

Management of Foci. No new ideas appeared; the same controversies prevailed.

Some still removed all possible foci,¹¹⁵⁷ but the majority agreed that only definitely infected foci should be removed,^{1487, 1601} and then not to cure the disease but to improve general health.^{784, 1370} Focal removal is only one link in the chain of therapy⁴⁹ to be recommended "with hope but without promise." Only occasionally does definite improvement follow eradication of an obvious local infection and then usually only in early cases when the onset has been temporally related to a definite infection (such as acute tonsillitis), the site of which can be removed. Well-developed arthritis rarely is benefited (Wetherby¹⁹¹⁶). Key⁹⁹¹ stated that the era of "promiscuous removal of foci" has passed, but Markson warned physicians not to shuttle too enthusiastically to the side of the "belittlers" in a reactionary shift from the older school. Opinions varied as to when foci should be eradicated. Some^{344, 434, 986, 1025, 1617} advocated early removal; others advised waiting until the disease quieted down or until the general health improved.^{1044, 1604, 1810}

1. Teeth. Devitalized teeth with roentgenographic evidence of periapical abscesses should be extracted.^{49, 527, 661, 690, 1509, 1816} The attitude toward devitalized

teeth with no periapical rarefaction was more conservative⁵²⁷; such teeth should be checked roentgenographically at intervals,⁶⁹⁰ and before extracting them the risk of interfering with nutrition by removing necessary masticating surface must be considered.¹⁹⁰¹ Deep pyorrheal pockets were thought to allow as much absorption as abscessed teeth or infected tonsil crypts⁵²⁷ and should be treated. Shuster claimed that 41 per cent of his 366 patients with early rheumatoid arthritis of less than six months' duration improved after removal of dental foci, but that in only 20 per cent of 215 advanced cases (arthritis of more than two years' duration) was improvement noted.

2. *Tonsils*. Recurrently inflamed tonsils should be removed.^{690, 1901, 1916} Shuster thought that tonsillectomy was of benefit in 50 per cent of 78 early cases and 25 per cent of 84 advanced cases. But Slocumb and his associates¹⁹²⁸ noted definite clinical improvement from tonsillectomy in only 5 per cent of cases in which infected tonsils were the only discoverable focus. [A high percentage of rheumatoid patients seen in private practice have had tonsillectomy long before the onset of their arthritis.—Ed.]

3. *Sinuses*. Gray warned that articular flare-ups may follow recurrent attacks of sinusitis and that chronic sinusitis should be treated. "Silent sinusitis" must be looked for,⁵⁷⁵ but Shuster obtained improvement following sinus surgery in only three of 24 early cases (12 per cent) and in only one (6 per cent) of 18 advanced cases.

4. *Gall-bladder, Intestines, Genitourinary System and Female Pelvis*. Evidence is distinctly against the importance of these sites as foci of infection according to Short and Bauer.¹⁹⁰¹ But the biliary tract^{632, 1079, 1907} and the colon⁸¹⁹ were considered as frequent sites of focal infection by some.

Vaccines. "Vaccines have made out a bad case for themselves."⁵⁰⁵ The trend now is away from their use, even by some formerly enthusiastic supporters.⁶⁰⁵ Such therapy "serves to keep the patient under regular observation and management,"¹⁷¹⁸ brings him "back to the office repeatedly,"¹⁹³⁸ and is useful "for psychotherapeutic purposes."¹⁶⁴³ Ormrod stated that vaccines were harmful because the patient is allowed to "drift into a hopeless and helpless condition" when better measures might have been used.

Proponents of vaccines are diminishing in numbers. Wetherby¹⁹¹⁶ continued to obtain results with intravenous use of streptococcus vaccine; of 1,192 patients so treated, clinical improvement was "definite" in 75 per cent. In another series 83 per cent of those receiving vaccine and 40 per cent of those receiving saline solutions were improved (Wetherby¹⁹¹⁵). Vaccines prepared from diphtheroids recovered from lymph nodes of patients with rheumatoid arthritis were used by Cadham; of 500 patients so treated, 37 recovered completely; 377 improved greatly, a total of more than 80 per cent returned to normal occupations. [Such surprising results would be more impressive if confirmed by others.—Ed.] With the use of streptococcus-staphylococcus combined antigen (streptococcus toxin-bacterial suspension combined with staphylococcus toxoid-bacterial suspension) 47 per cent of 34 patients resumed work and 29 per cent more showed improvement.¹⁸⁷⁵ But Parker's results with Crowe's vaccine were no better than results from injections of normal saline. [Evidently almost any old vaccine works.—Ed.]

Foreign Proteins. Injections of triple typhoid vaccine to produce foreign protein reactions and "general stimulation of metabolism" were recommended for selected cases.^{302, 633, 1094, 1177, 1487, 1755} Wetherby¹⁹¹⁶ was not impressed with such therapy, and Key⁹⁹⁴ stated that in early active cases it often aggravates rather than benefits. Two sudden fatal reactions were recorded (Love and Driscoll; Urbach). At necropsy in both cases [one of rheumatoid arthritis; one

of choroiditis.—Ed.] findings resembled the Sanarelli-Schwartzman phenomenon noted in experimental animals: widespread cutaneous and visceral petechiae; intense congestion of lungs and intestines, and renal, hepatic and adrenal necrosis. Two cases of severe renal irritation (gross hematuria, marked reduction in renal function) after typhoid vaccine therapy were reported (Taylor and Page); both patients had pre-existing renal disease but no arthritis. A patient who had been taking cinchophen had fatal acute yellow atrophy of liver after two intravenous injections of typhoid vaccine; recent cinchophen therapy was therefore considered a contraindication for typhoid vaccine (Yott).

Bee Venom. Only five of 24 patients treated by Hollander were notably improved. Results were considered "very discouraging." [We agree.—Ed.] Banghart was more encouraged; nine of 16 patients were markedly improved, five moderately improved. [Only two failures?—Ed.] Bee venom acts only as an analgesic; comparable results were obtained with injections of magnesium sulfate (12.5 per cent ³⁴³).

Cobra Venom. The use of cobra venom to control pain of rheumatoid arthritis was disappointing to Talkov and Bauer. Only three of 12 patients experienced transient relief; no objective improvement resulted. Acetylsalicylic acid was found to be a better analgesic. But Albee and Maier reported satisfactory relief in 28 of 32 patients.

Diet. Most patients with rheumatoid arthritis lose weight; hence, a high caloric diet complemented with adequate vitamins and minerals is indicated.^{46, 567, 606, 784, 1294, 1372, 1487, 1620} Pemberton and Scull¹³⁷³ estimated that the diet for afebrile arthritic patients of essentially normal weight at rest in bed should contain a caloric value of about 10 per cent more than the calculated basal energy transformation. One author¹⁸²² claimed that certain patients with "arthritis" were greatly benefited by eliminating food to which they reacted allergically by cutaneous tests.

Vitamins. The daily vitamin requirement of patients with rheumatoid arthritis may actually be above normal (Kuhns¹⁰⁴⁴). However, there is no known antirheumatic vitamin, nor has it been shown that any vitamin has a direct relationship to the disease. Vitamin therapy at most is only a "booster" to general health, not a specific remedy for arthritis.

1. *Vitamin A.* The course of the disease is apparently not altered if a coexisting vitamin A deficiency is corrected.^{605, 994}

2. *Vitamin B.* Supplemental vitamin therapy with the elements of the B complex may improve general health. Because painful neuritis may often be relieved dramatically by thiamine chloride, it was hoped that the pain of rheumatoid arthritis might be relieved also; but massive doses of thiamine were ineffective (Freyberg^{605, 606}; Key⁹⁹⁴).

3. *Vitamin C.* Although ascorbic acid levels in blood plasma are frequently subnormal, the disease was not altered even when "the blood was kept saturated with vitamin C for periods of three months or more" (Key⁹⁹⁴).

4. *Vitamin D.* Although used unenthusiastically since 1935 and previously unheralded, high potency vitamin D therapy has currently become a "popular" treatment for rheumatoid arthritis because of recent "flamboyant advertising"⁴¹⁶ and publicity which "overemphasizes part truths and overlooks the rest of available information."¹⁶²⁰ Vitamin D in large doses may provide subjective improvement (reduction in pain) in some cases of rheumatoid arthritis (Steck). Seven (50 per cent) of 14 patients treated by Slocumb¹⁶²⁶ with daily doses rang-

ing from 52,500 to 386,000 units noted some subjective relief, but few or no objective changes. Freyberg^{605, 606} noted some subjective relief in 14 (39 per cent) of 36 patients, objective improvement in only six (17 per cent). Reductions in sedimentation rates of erythrocytes and alterations in the clinical course were rarely noted. Wagner evaluated end results one year after massive vitamin D therapy. Of 32 cases, results were "excellent" in five, good in two, fair in 18, poor in two, and none in five (i.e., notable in only seven cases, 22 per cent).

Many believed this treatment to be of little value.^{180, 968, 994, 1718} Boots obtained as good results with plain cod liver oil given as a tonic. But some^{542, 1084, 1085} remained enthusiastic. Snyder, Squires and associates^{1659, 1660, 1001, 1062, 1806} noted objective improvement more often than others and claimed partial or complete remissions in about 60 per cent of cases.

[De Kruif's⁴⁵⁷ enthusiastic article about vitamin D and ertron in "The Readers Digest" entitled "Hope for the victims of arthritis" might better have been called "False hope for the victims of arthritis": so wrote certain commentators.^{180, 416} We agree.—Ed.]

Massive vitamin D therapy is not without danger.^{505, 1044} Although it takes three to six months after withdrawal for the serum concentration of vitamin D to fall to normal,¹⁸⁷² toxic symptoms usually subside quickly after administration is stopped. Early signs of toxicity (sweet taste, nausea, vomiting, polyuria, polydipsia, occipital headache) were discussed (Slocumb and Polley¹⁶²⁰). Severe renal damage from deposition of calcium in renal parenchyma with resultant azotemia, albuminuria and cylindruria may result if these symptoms are ignored; two such cases, one with extensive ectopic calcification about joints, were reported.⁴³² Toxic reactions were said to be encountered less often with the electrically activated vaporized sterol (Whittier process) than with ultraviolet irradiated ergosterol (Steenbock process^{1452, 1662}). Others stated that ertron is also capable of toxicity.^{505, 1186} [Severe, even fatal, toxicity has also accompanied the use of "ertron."—Ed.]

5. *Vitamin E.* In 22 cases rheumatoid arthritis was treated with wheat germ oil (4 to 8 c.c. daily) for six to 18 months.¹⁷³² "Definite improvement" was claimed in 77 per cent. [The "inevitable 75 per cent!"—Ed.]

Endocrines. Results from use of estrogen in a few cases of rheumatoid arthritis (males or females) were satisfactory to some,^{1138, 1282, 1732} not to others.^{605, 1625}

Transfusions; Hematonics. Repeated blood transfusions may sometimes initiate a remission⁷⁸¹ when marked anemia (values for hemoglobin of less than 10 gm.) will not respond to iron salts.^{523, 1629}

Vasodilators: Histamine; Choline and Others. Transient symptomatic relief may follow the introduction of vasodilating drugs, histamine and acetyl- β -methylcholine chloride (mecholyl chloride), into the skin by iontophoresis.¹⁶⁷¹ Smith and Freyberg noted some subjective improvement "for a short time" in 79 per cent of 28 patients so treated but on reexamination only 11 per cent maintained any improvement; few had objective improvement. Such treatment is useful only when small joints are involved,¹¹²⁰ when local heat cannot be tolerated because of paresthesia¹⁰⁸² or hot weather¹⁰³¹ and when hyperemia fails to result from simpler methods.¹⁴⁸⁷ But "great symptomatic relief" in arthritis (unspecified as to type) was claimed by others.^{779, 1448} Repeated lumbar paravertebral blocks with procaine hydrochloride to produce vasodilatation were recommended for persistently painful joints of lower extremities.¹²⁸⁸ Nicotinic acid was given both orally and intravenously in large doses

for its vasodilating effect to 35 patients with rheumatoid arthritis (Kurtz). Intravenous dosage consisted usually of 200 to 400 c.c. of a 0.05 per cent solution. Oral dosage consisted of 50 to 200 mg. every 15 minutes for three doses twice daily. Significant subjective improvement was claimed in 15 of 35 cases and marked or moderate objective improvement in 26. [Criteria for improvement, duration of results and follow-up studies were lacking.—Ed.]

Sulfur. Treatment with sulfur has been discontinued in most clinics.²⁰⁰ Freyberg⁶⁰⁶ concluded: (1) no sulfur deficiency or abnormality of sulfur metabolism exists in arthritic patients, and (2) there is no biochemical or metabolic indication for, or benefit from sulfur medication in arthritis.

Sulfonamides. These proved useless in rheumatoid arthritis.^{175, 1825}

Penicillin. Because of the effectiveness of penicillin against a variety of infectious agents, especially hemolytic streptococci, many were hopeful that it might prove effective against rheumatoid arthritis. Boland, Headley and Hensch gave penicillin daily for 10 to 14 days (daily doses from 120,000 to 320,000 Oxford units and total doses from 1,800,000 to 3,250,000 units) to 10 soldiers with early progressive rheumatoid arthritis: results were negative. Of the 10 patients seven did not improve, one was worse, one showed slight subjective but no objective improvement, and one demonstrated moderate objective and subjective improvement in some, but not all, involved joints. Because of the capricious nature of rheumatoid arthritis the improvement in the two cases was regarded as unrelated to the penicillin. In view of the negative results these authors concluded: "It does not seem unreasonable to assume that rheumatoid arthritis is not caused by any of the bacteria which are already known to be rapidly affected by penicillin." Comroe's results³⁶⁵ were similar. Six patients given total doses of 1,400,000 to 3,300,000 units (for two to four weeks) received no benefit. Penicillin administered intramuscularly to rheumatoid arthritics was found to penetrate rapidly into joint fluid and to attain levels comparable to those in blood serum.⁶³ Maximal antibacterial quantities persisted longer in joint fluid than in blood serum, but penicillin did not accumulate in joint fluid.

Bile Salts; Liver Extract. No new data appeared.

Analgesics. Much comfort usually can be obtained from the wise use of analgesics. Salicylates are usually more effective than other drugs.^{600, 1070, 1157, 1643, 1908} Patients can go on taking 40 to 60 grains (2.6 to 4 gm.) of acetylsalicylic acid daily without apparent harm.^{170, 418} Calcium acetylsalicylate (cal-samate) produced less gastric irritation in animals than did acetylsalicylic acid.¹⁷⁴⁴ Acetophenetidin is sometimes more effective than salicylates¹⁰¹⁰; after review of the literature Cohen³⁴⁰ concluded that "little or no evidence exists to justify the inclusion of acetophenetidin in the category of dangerous drugs." The dangers of cinchophen were again mentioned.⁴¹⁸

Demerol, a new synthetic analgesic which approaches the potency of morphine, given parenterally in 100 mg. doses every four hours, usually controlled rheumatic pain of any severity (Batterman). Given orally, "complete relief" was achieved for seven of 14 ambulatory patients with rheumatoid arthritis; about the same results were obtained regardless of whether 50, 75 or 100 mg. doses were given. Ambulatory patients often experienced unpleasant side reactions (dizziness, nausea, vomiting, rarely syncope). Liability to addiction exists although much less so than with opium derivatives. [Because of the liability to addiction we cannot recommend its use for such a chronic disease as rheumatoid arthritis.—Ed.]

Antireticulocytotoxic Serum. The "A.C.B. serum" of Bogomoletz ("anti-reticulocytotoxic serum," "Russian serum") was used unsuccessfully by Bach.⁴⁸

This serum is produced by immunizing horses with cells of spleen and bone marrow obtained from a human corpse. Presumably antibodies so produced "stimulate" or "block" the reticuloendothelial cells of the recipient. The serum is supposed to "intensify immunity," using "the recipient's tissue as antigens." As a result "the complement in the blood and the opsonic index are increased," and "the sedimentation rate falls if increased, and increases if low." It is said not to act directly on microorganisms but on "the reactivity of the physiological system of the connective tissue," "the condition of which determines the destruction of pathogenic organisms and their toxins." Bogomoletz claimed success in the treatment of "rheumatism," or "acute arthritis" unidentified as to type.¹⁹⁵¹ Bach⁴⁸ treated 35 patients with rheumatoid arthritis: improvement was noted in only three. Two of the three patients who improved were "tired Lambeth women" admitted to the hospital for a rest, who received the serum at once; two months later both had had relapses. The third patient had "a marked psychogenic factor"; two months after dismissal she was readmitted, this time being relieved by two injections of distilled water. [One of us, R. H. F., has also been disappointed with his results from this serum in rheumatoid arthritis.—Ed.]

Miscellaneous. The night cramps in calf muscles of patients with either rheumatoid or osteoarthritis were relieved by one daily dose of quinine sulfate (3 grains or 0.2 gm.) at bedtime.⁶⁸⁰ Chaulmoogra oil still had one advocate.²⁵⁹ Histaminase was tried "without startling results" (Muether). Crowe⁴¹² injected 1 per cent acid phosphate into 280 swollen painful joints and claimed "lasting relief" in three fifths and "temporary relief" in all the rest except one. Good results in arthritis were claimed with "systemic disinfection" using "thyroid substance and potassium permanganate."¹³⁰⁷ Nott stated "this treatment has been before the medical profession for seventeen and a half years without one word being published against it." [Shall we be the first to do so?—Ed.] "Eaton's formulae," concoctions containing cinchophen and neocinchophen in combination with methenamine, sodium cacodylate and so forth, as well as "imperial draught" were described.⁴⁰⁵

Spinal "Pumping." Rheumatoid arthritis is a neurodystrophy according to Speransky (1935). For curious reasons (discussed under "Treatment of Rheumatic Fever") he applied spinal pumping to 15 patients with "chronic arthritis": four recovered; nine improved; two did not. The Gillmans⁶⁵³ used spinal pumping in connection with salicylates given orally: 60 patients with "various types of rheumatoid arthritis" were treated. "Improvement" was often noted within 24 to 48 hours and was sometimes "striking" within four hours of the pumping. Reportedly 80 per cent of the patients with subacute disease (numbers not stated) were "discharged as cured at the end of three days." [Most difficult to believe.—Ed.] Relapses were "not uncommon."

[The Gillmans⁶⁵⁴ recently made a second report on results in 70 cases of various rheumatic diseases including 22 of "chronic arthritis." As in the previous report the terminology used was vague, claims made seemed extravagant; the rationale unacceptable. The procedure may not be without danger: one death occurred.—Ed.]

Neostigmine (Prostigmine). This was used by Trommer and Cohen in 19 cases of rheumatoid arthritis with "a maximum of deformity but a minimum of active joint involvement." A test dose of 0.5 mg. of neostigmine methylsulfate and 0.6 mg. of atropine sulfate was usually first given, then daily maintenance oral doses of neostigmine bromide (7.5 to 45 mg.) with tincture of belladonna (0.6 to 1.2 c.c.). Marked relaxation of muscle spasm, increased motion and relief of pain from muscle spasm (but not relief of articular pain) were claimed

in 16 of 19 cases. When the drug was given subcutaneously, beneficial effects were said to occur within 15 minutes and to persist for several days (Cohen⁵⁴¹). But prostigmine produced a "depressing effect" on the atrophying muscles of animals with experimental chemical arthritis.⁶¹⁸

[The early favorable results from use of neostigmine for neuromuscular dysfunction were editorially considered "insufficient for critical evaluation."⁵⁰⁷ However, neostigmine was De Kruijff's⁴⁵⁸ arthritis remedy for 1946. His misleading over-optimism also was criticized in an editorial.⁵⁰⁸ More recently Cohen, Trommer and Goldman reported that neostigmine is inferior to physostigmine. At the 1946 meeting of the American Rheumatism Association several speakers (Pemberton, Lewin, A. S. Gordon, Traeger, Freyberg, C. J. Smyth) expressed disappointment with this type of treatment.—Ed.]

Chrysotherapy. Gold is still extensively used after 20 years of trial and error. The exact value of gold salts in the treatment of rheumatoid arthritis remains uncertain but rheumatologists of experience, with few exceptions, report results therefrom better than those obtained with any other single remedy.

1. Indications. Because of the toxicity of gold salts American physicians until recently have restricted their use to cases of rheumatoid arthritis not amenable to more conservative measures. This practice is still adhered to by some,^{366, 1513, 1509, 1629, 1604, 1910} but others have recommended early use of gold.^{307, 739, 781, 1648, 1713, 1946} Chances for complete remissions appear to be better if chrysotherapy is used early (Cecil³⁰⁴), and some believed that to delay until other forms of treatment have failed is an unjustifiable waste of time (Cohen, Goldman and Dubbs) which permits unnecessary discomfort and the development of irreparable joint damage.¹⁴⁷⁷ Others urged that chrysotherapy be delayed for at least three to six months after the onset of rheumatoid arthritis or until the likelihood of spontaneous remissions seemed remote.^{1500, 1664, 1713} Extreme views were expressed by Robinson¹⁴⁷⁸ who stated that gold should be used in any case of rheumatoid arthritis in which the sedimentation rate is elevated, and by Key⁹⁰⁴ who stated that "it should be employed in every case." Gold salts should not be used in any rheumatic disease other than rheumatoid arthritis, with the possible exception of psoriatic arthritis.^{366, 686, 1664}

2. Contraindications. Contraindications listed were severe diabetes mellitus, nephritis, ulcerative colitis, hepatic insufficiency, blood dyscrasias and hemorrhagic tendencies.^{1648, 1713, 1715, 1946} Allergy,¹⁰⁴¹ pregnancy⁶⁸⁰ and history of exfoliative dermatitis³⁰⁶ were also mentioned, but hypertension was not considered a contraindication.¹⁷¹³ Hartung⁷⁸¹ warned against chrysotherapy in the presence of associated acute rheumatic fever with or without carditis, or of disseminated lupus erythematosus (in contradistinction to the discoid type in which gold salts may be employed).

3. Preparations. Several preparations of gold salt are now marketed. Those usually used in the United States are listed in table 3.^{607, 784, 1661}

Colloidal gold preparations, including the sulfide, being of little therapeutic value⁶⁰⁷ have generally been discarded (Freyberg, Block and Levey⁶¹⁰).

4. Dosage and Methods of Administration. Most preparations are given intramuscularly; gold sodium thiosulfate may be given intravenously. Gold is the active principle and since the gold content differs in various salts, dosage must be figured in equivalent doses of gold.⁶⁰⁷ A favored schedule of treatment with myochrysine (50 per cent gold) has been to inject increasing amounts of the salt, from 10 mg. to 100 mg. weekly, until a total of 1 to 1.5 gm. has been given. Gold thioglucose (solganal-B oleosum) also contains 50 per cent gold, but is absorbed less readily and to have an equal amount of gold retained about 125 per cent of the dose for myochrysine is re-

TABLE III
Gold Salts Available in the United States

Chemical Name	Proprietary Name	Solubility in Water	Physical State	Gold Content, Per cent
Gold sodium thiosulfate	Sanochrysine	+	Aqueous solution	37
Gold sodium thiomalate	Myochrysine	+	Aqueous solution	50
Gold calcium thiomalate	Calcium aurothiomalate	—	Oil suspension	50
Gold thio-glucose	Solganal-B oleosum	+	Oil suspension	50
Gold thioglycolanilide	Lauron	—	Oil suspension	54

quired (Freyberg⁶⁰⁶). Gold thiosulfate is only 37 per cent gold, hence proportionately larger doses are needed. Because fewer toxic reactions result from smaller weekly doses, most authorities do not give more than 50 mg. of gold salt (about 25 mg. of gold) per week (e.g., myochrysine and solganal-B oleosum).^{739, 740, 784, 1754, 1916} Freyberg⁶⁰⁶ found that weekly doses of 50 mg. of gold salts were as effective as doses of 100 mg., but that weekly doses of 25 mg. gave inferior results. Others (Buttorff²⁷¹; Rawls and associates¹⁴³⁸) claimed equally good results with doses not exceeding 25 mg. (solganal-B oleosum) per week. Usual practice has been to give one, two or more courses of gold salts (total 1,000 to 2,000 mg. each course) with rest-periods of two to six months between courses. The frequency of relapses during rest-intervals prompted Freyberg and his colleagues,⁹¹³ Boots and Ragan, and others to give a single course followed by small maintenance doses every week or so for several months longer. [The plan of continuing maintenance doses has now been widely adopted.—Ed.] Much larger doses of a newer preparation, gold thioglycolanilide (lauron), claimed to be substantially less toxic, were recommended.^{1479, 1713} Robinson¹⁴⁷⁹ advocated initial doses of 25 mg.; then he gradually increased the weekly dose to as high as 300 mg. Total doses as great as 3,750 mg. in one course were given. [Two of us, D.C.C. and R.H.F., have noted severe skin reactions to lauron. Those who have studied the metabolism of gold salts find it difficult to understand how any "insoluble" gold compound such as gold thioglycolanilide (lauron) can be depended on to give consistent results. With such salts speed and amount of absorption and elimination vary widely, and when they are not tolerated prolonged toxic reactions may occur. Even if they were nontoxic, the use of such large doses is difficult to rationalize. Before they are considered superior to the aqueous soluble preparations, such insoluble compounds must provide greater benefits than have yet been reported.—Ed.]

5. *Mode of Action.* Our knowledge of the metabolism of gold salts is much greater than it was five years ago, still "it is not known where, how or why gold salt therapy works" (Freyberg⁶⁰⁷). Hartung found no evidence that gold salts stimulate the reticuloendothelial system or increase blood agglutinins. Gold sodium thiomalate (myochrysine) was an effective chemotherapeutic agent in the prevention of arthritis produced in rats by hemolytic streptococci, but the preventive dose was close to the lethal dose, and gold was not as effective prophylactically as either sulfanilamide or sulfathiazole, nor did it cure the disease once it was established.¹⁵¹² Gold sodium thiomalate is bactericidal in vitro against hemolytic streptococci, type green, in dilutions through 0.000001 per cent and bacteriostatic in higher dilutions.⁷⁸⁵ Other common organisms (*Staphylococcus albus*, *Staphylococcus aureus*, nonhemolytic streptococci, pneumococci, types III and VI) are somewhat similarly affected. In vitro bacteriostasis was roughly proportional to the concentration of gold salt. The bacteriostatic

powers of the patient's serum are markedly increased ⁷⁶⁵ against hemolytic streptococci, type green, after administration of gold sodium thiomalate, but agglutination titers for this organism are not increased. But since the cause of the disease or the offending organism (if any) has not been demonstrated, it cannot be assumed that clinical results from gold are due to its bacteriostatic effect.¹⁰²⁹

Sabin and Warren demonstrated that on the pleuropneumonia-like arthritis of mice gold compounds whether inorganic or organic, soluble or insoluble, were capable of exerting a curative effect. But colloidal gold had no therapeutic value. The earlier the arthritis in mice was treated, the more rapid and complete was the response. When treatment was delayed for as long as four weeks (coinciding with the stage of cartilage destruction) the involvement in some joints was irreparable. When the total dose was administered in a week, better results were obtained than when smaller doses were given for a longer period. The experimental arthritis disappeared completely in 96 per cent of 171 mice treated with adequate doses at the proper time.

When glutathione, cysteine or thioglycolic acid is given in aqueous solution with gold salts, their SH group is blockaded, and they do not give the characteristic reaction with sodium nitroprusside, the usual reagent for the SH radical.¹⁰⁰⁸ Libenson proposed: "Since glutathione and cysteine are present in most of the organic tissues, it can be assumed that the gold compounds, either ionic without sulfur or complex gold-sulfur compounds, given parenterally combine with the SH radicals contained in the cells and exert their therapeutic action later as gold-glutathione or gold-cysteine complex compounds." But Preston, Block and Freyberg demonstrated in arthritis of mice that the effectiveness of gold compounds is not dependent on a sulfhydryl linkage. Both gold sodium thiomalate (containing sulfur in sulfhydryl linkage) and gold sodium succinimide (containing no sulfur) were effective in curing experimental arthritis. Sodium thiomalate and the disulfide form of sodium thiomalate (neither containing gold) were ineffective; thus it is the gold rather than the sulfur in the gold salts which is the effective element (Sabin).

Block, Buchanan and Freyberg ^{156, 157} studied the absorption, distribution and excretion of various compounds of gold in rats. Absorption, after intramuscular administration, was related to the physical properties: colloidal preparations (colloidal gold, colloidal gold sulfide) were poorly absorbed as compared to crystalline salts (gold sodium thiosulfate, gold sodium thiomalate, gold sodium succinimide). Following injections, gold was found in kidneys and liver in larger amounts than in other organs. When crystalline salts were injected, gold was found in greater amounts in kidneys, whereas with colloidal preparations gold was more abundant in the liver. The urine was the chief route of excretion of crystalline preparations; the feces, the chief route for colloidal gold. When intramuscular injections of soluble crystalline salts (myochrysin, solganal-B oleosum and gold sodium thiosulfate) were given in increasing weekly amounts, a steplike increase in plasma gold concentration resulted. When weekly doses were kept constant (50 mg. of gold, 100 mg. of gold salts) the concentration in plasma remained relatively constant, usually between 0.4 and 0.8 mg. per 100 c.c. During the period of administration much gold was retained: when weekly injections of 50 mg. of gold (100 mg. of the salt) were given, the average daily excretion of gold was only 1 mg., or slightly more (7 to 10 mg. weekly). Hence, during treatment with crystalline salts about 80 per cent of injected gold remained in the body. After a course of treatment, gold was found in plasma and urine for six to 12 months.⁷⁶⁶ After injections of insoluble colloidal gold sulfide, which is therapeutically ineffective, little or no gold was found in plasma, small amounts in feces, and none or only traces in urine; the colloidal particles were phagocytized in large amounts by reticuloendothelium, especially in liver and spleen.^{613, 1524}

In vitro studies of oxygen consumption by hepatic and renal tissues as influenced by various gold-containing compounds revealed that the inorganic ionizable compounds

(gold chloride, gold sodium thiosulfate, colloidal gold sulfide) inhibited oxygen consumption, while the organic nonionizable compounds (gold sodium succinimide, gold sodium thiomalate, gold thioglucose) did not.¹⁵⁸ Plasma lipids in cases of active rheumatoid arthritis deviated little or not at all from normal before, during and after chrysotherapy (Bayles and Ridell). [These excellent, important studies on the metabolism of gold by Freyberg, Hartung, Sabin and their colleagues have done much to make chrysotherapy more rational and safe.—Ed.]

6. *Results from Chrysotherapy.* Bayles and Hall devised a "yardstick" to evaluate results of therapy in rheumatoid arthritis, particularly chrysotherapy. The following criteria were used: functional activity, activity of disease, degree of deformity, sedimentation rate, hemoglobin value, and body weight. [If some workers would use these or similar criteria, they would refrain from publishing vague, uncontrolled and unconfirmable results.—Ed.]

In 100 cases in which follow-up observations for periods of six months to two years were available, the following results of treatment with myochrysine were reported by Dawson, Boots and Tyson: complete arrest in 22, marked improvement in 29, "moderate but very real improvement" in 25, slight improvement in 10, no improvement in 14. Relapses occurred in 12 per cent of cases strikingly improved but the original degree of activity was resumed in "very few." Loge-feil and Hoffman reported complete arrest or marked improvement in 65 per cent of 74 patients treated with a single course of gold thiosulfate intravenously (50 mg. twice weekly; total dose of 1,000 mg.). The relapse rate was 15.4 per cent. Treating 250 patients with solganal-B oleosum (graded doses from 10 to 100 mg. and total dose of 1,200 mg.) Gardner noted that 70 to 80 per cent were improved and that 50 per cent of those recently affected and 30 per cent of those affected more than two years were cured. [The number "cured" was not stated. This report seems unduly optimistic.—Ed.] Smyth and Freyberg¹⁶⁴⁸ found myochrysine and gold sodium thiosulfate to be equally effective; 66 per cent of 53 patients treated with the former and 64 per cent of 11 patients treated with the latter showed moderate or marked improvement or arrest of the disease. Only 25 per cent of 12 patients given colloidal gold sulfide were notably improved.

Cecil, Kammerer and De Prume treated 235 patients: 207 with myochrysine, 40 with solganal-B oleosum, and three with gold sodium thiosulfate. [This totals 250 since some patients received more than one salt.—Ed.] Results were complete remission in 31 per cent, great improvement in 35 per cent, moderate improvement in 20 per cent, no improvement in 14 per cent. Best results were obtained in early cases: in 78 per cent of early cases and 62 per cent of late cases remissions or great improvement occurred. Thirty-four per cent of the patients with remissions and 50 per cent of those "greatly improved" had relapses in from six months to five years; about 50 per cent of the relapses occurred within one year. In only half of those in whom relapses occurred did the disease become inactive again with a second course. In another series 60 per cent of 101 patients treated (91 with myochrysine; 10 with solganal-B oleosum) showed moderate or marked improvement (Price and Leichtentritt). Results depended on the severity of the disease; significant improvement was obtained in 93 per cent of cases of mild disease, 80 per cent of moderate, and 40 per cent of the severe. Graham and Fletcher reported results in 100 cases in which myochrysine was given in doses of 10 to 100 mg. per week (total of 1.06 gm.). Complete remissions were obtained in 16 per cent, marked improvement in 51, some improvement in 20 and

no improvement in 13 per cent. Best results were obtained early in the course and in younger persons. In 54 per cent of 264 cases in which Hartung⁷⁸⁴ used myochrysine, remissions were observed but subsequent relapses occurred in 21 per cent; this left 33 per cent in which complete arrest was maintained after one year.

"Improvement of a sort" was obtained in 87 per cent of 122 patients treated by Cohen and Dubbs with solganal-B oleosum (1.24 gm. per course): 35 per cent showed only subjective improvement; 17 per cent were "much improved"; 36 per cent were "very much improved"; 9 per cent showed no change; 4 per cent were worse. [This totals 101 per cent.—Ed.] Summarizing later the results of 417 courses of treatment given 259 patients Cohen, Goldman and Dubbs³⁴⁴ reported "very marked improvement" in 48 per cent, "marked improvement" in 18 per cent. Rawls and his associates,¹⁴³⁸ using small doses of solganal-B oleosum (25 mg. per week), obtained results which compared favorably to those obtained with larger doses. Definite courses were not given; if improvement occurred, gold salts were used indefinitely, or for at least 12 months. Such a schedule reduced the incidence of relapses. For patients who failed to respond adequately to 25 mg. weekly, the dosage was increased to 35 or 50 mg., but never to more than 50 mg. In 53 of 100 cases the arthritis was markedly improved or inactivated; in 21 definitely improved; in 26 improved slightly or not at all.

Fraser⁵⁹¹ treated 57 patients with myochrysine (one or two courses of 1 gm. each) and 46 controls with injections of a therapeutically inert "control substance." Clinical signs of notable improvement occurred in 63 per cent of those who received gold salts, in only 21 per cent of the controls. Degrees of improvement in the two groups were in greater contrast: "great improvement" occurred in 42 per cent of those given gold and in only 8 per cent of the controls. Moreover, in 18 per cent of the former and 55 per cent of the controls the disease remained stationary or became worse. [This study deserves special attention as it and that of Ellman, Lawrence and Thorold (1940) constitute the only two reports on gold therapy which mention controls so far as we know.—Ed.] Robinson¹⁴⁷⁸ treated 200 patients with myochrysine. "Approximately 25 per cent" were "cured," about 25 per cent were greatly improved, about 25 per cent showed some improvement, and the remaining 25 per cent were not helped.

Short's¹⁵⁹⁸ results with chrysotherapy contrasted to those of others; only six (19 per cent) of 31 patients showed noteworthy subjective and objective improvement, and three of these later had relapses. Stengel treated 30 patients with gold thioglycolanilide (lauron); in three cases (10 per cent) the disease was arrested; in 17 (57 per cent) markedly improved, in seven (23 per cent) moderately improved, and in three (10 per cent) worse. Using gold calcium thiomalate (50 mg. weekly for 12 injections; total dose 600 mg.) Ray¹⁴⁴⁰ found that 50 per cent of 50 patients showed definite improvement; 25 per cent were somewhat improved; and 25 per cent noted no change.

7. Toxic Reactions. The usual toxic reactions (dermatitis, mild rash to exfoliative type, ulcerative stomatitis, ulcerative colitis, hepatitis, thrombocytopenic purpura, agranulocytosis, aplastic anemia, bronchitis, and so forth) were encountered.^{342, 591, 628, 739, 1122, 1400, 1569, 1629, 1701, 1946} Usually they did not occur until after several hundred milligrams of the drug had been given⁶⁰⁶ but they may occur after small initial doses (20 to 30 mg.), during a second or third series, or even weeks after

treatment is completed.¹⁶⁶⁵ All but one worker encountered toxic reactions; Stengel, using lauron reportedly had none in 30 cases. Ten writers reported the percentages of reactions in their cases; they averaged 37 per cent, ranging from 8 to 61. Most reactions were minor and disappeared promptly on discontinuance of the treatment. Serious reactions occurred in not more than 5 to 10 per cent of cases.⁴⁵⁰ Short,¹⁸⁹⁸ reviewing earlier literature, found the mortality rate in a combined series of 1,800 cases to be one in 200 cases (0.5 per cent), a rate 10 times higher than for neoarsphenamine in the treatment of syphilis. But Hartung noted only one death in "well over 1,000 cases." Cecil, Kammerer and De Prume had one death (ulcerative enteritis) in 245 cases; Dawson, Boots and Tyson had one from thrombocytopenic purpura in 101 cases. A death from multiple cerebral hemorrhages after chrysotherapy was reported¹⁶⁶⁵: 0.10 gm. of brain tissue contained 0.035 mg. of gold, "a very appreciable figure." In two cases latent syphilis was thought to have been reactivated by chrysotherapy.¹³⁴⁰ [The mortality rate in all reported cases has been about one in 250 cases (0.4 per cent), but the incidence of serious or fatal reactions is expected to be lowered materially by the use of BAL.—Ed.]

Little is known regarding the nature of the reactions; they probably reflect something other than simple intoxication from a heavy metal.¹⁴⁰⁰ In the blood gold is combined intimately with serum protein; perhaps gold proteinate may be allergenic in persons in whom toxic reactions develop.⁶¹² Libenson suggested that toxicity might result from the action of gold on the organic sulfhydryl compounds of the body; by blocking the SH groups of glutathione, cysteine and other sulfhydryl compounds, the normal oxygen-reduction process in cells may be prevented.

8. *Prevention and Treatment of Toxic Reactions.* No constant indicator signals the approach of a toxic reaction (Rosenberg). Skin tests are of no help (Lintz). A drop in the platelet count to less than 75,000 per cubic millimeter, a fall in the leukocyte count to less than 4,000, eosinophilia, albuminuria, microscopic hematuria and pruritus have all been designated as danger signs. [But they are not constantly reliable.—Ed.] To minimize the frequency of reactions certain precautions should be taken⁷⁸⁴; before each injection ascertain whether a rash or purpuric spots, stomatitis, albuminuria or microscopic hematuria is present; every two weeks obtain leukocyte and differential counts and hemoglobin determination; for "susceptibles" obtain Addis and platelet counts. Gold should not be given by a physician unless he is familiar with the bad as well as the good results (Slocumb and Polley¹⁶²⁰). Severity and frequency of reactions are reduced when the smaller weekly doses of gold salts are used.^{271, 1438} Freyberg⁶⁰⁶ noted the following incidences of toxic reactions in relation to dosage: 100 mg. of gold salt per week, 41 per cent; 50 mg. per week, 30 per cent; 25 mg. per week, 18 per cent.

Tarsy¹⁷⁷⁴ administered "detoxicants" (glycine, cystine, glucuronic and ascorbic acids and choline) to patients under chrysotherapy, but they failed to prevent toxic reactions. Neither vitamin B complex nor cevitanic acid exerted any preventive influence (Cohen³⁴⁴).

Apparently there is no means of altering the metabolism of gold to lessen toxic reactions once they occur. "Anyone using the drug is at its mercy" (Freyberg⁶⁰⁶). Minor reactions were treated with nicotinic acid and cevitanic acid with questionable efficacy. For exfoliative dermatitis sodium thiosulfate and calcium salts were recommended (Lintz).

[Until recently these remarks were true. But current results with the use of BAL (British Anti-Lewisite) lead us to hope that an effective method for controlling

at least some of the serious toxic reactions is at hand.^{345, 1116, 1426} Nine patients who had exfoliative dermatitis of less than two months' duration, one who had severe thrombocytopenic purpura and one who had granulocytopenia responded rapidly to intramuscular injections of BAL. One patient whose dermatitis had been present for three months was not relieved. Penicillin is also a potent weapon against granulocytopenia which may result from chrysotherapy.¹⁷⁵ These results are indeed promising but should not encourage physicians to lower their guards unduly or prematurely against the hazards of chrysotherapy.—Ed.]

9. *Newer Gold Preparations.* Determined to find an effective, yet relatively nontoxic preparation, physicians have continued to try new salts of gold. Whereas, the therapeutic value of soluble gold salts seems to depend chiefly on the concentration of gold, the toxicity apparently is influenced by the nature of the attached radical and by the solubility or relative insolubility of the compound. An insoluble preparation, calcium aurothiomalate, was found by Sabin to be relatively nontoxic (as measured by lethal effect on mice) and as therapeutically effective in arthritis of mice as sodium aurothiomalate (myochrysine). In humans this preparation apparently was devoid of organ-toxicity but reactions in skin and mucous membrane did occur. [Some were severe.—Ed.] Calcium aurothiomalate was found by Ray¹⁴⁴⁰ to be about as effective as soluble preparations. More recently gold thioglycolanilide (lauro) has been marketed. According to some (Robinson¹⁴⁷⁹; Stengel) this compound is "superior to other gold compounds in its beneficial effects" and "far less toxic." Although larger individual doses of the compound were used (up to 311 mg.), three of 55 patients treated by Robinson¹⁴⁷⁸ had "a slight rash," one an abscess of the buttock and several a "mild sore mouth"; no other toxicity was noted. [Some of us have had considerable clinical experience with this compound and have noted mild albuminuria and severe prolonged dermatitis. In our opinion it possesses no special therapeutic advantage and all the potential disadvantages of other commercial gold preparations.—Ed.]

10. *Conclusions on Chrysotherapy.* Chrysotherapy offers greater promise than any other form of therapy according to Dawson, Boots and Tyson, but they warned of its dangers. When carefully given its good effects far outweigh the risk involved (Hartung⁷⁸⁴). Wetherby¹⁹¹⁶ considered the results from gold therapy encouraging, "although like vaccine it has only occasionally been followed by clinical cure when used in patients with a well-established arthritic process." In the experience of Smyth and Freyberg¹⁰⁴⁸ gold therapy was "valuable in many cases" but "not uniformly beneficial" and "its potential toxicity is a definite objection to general use." Several^{434, 591, 660, 739, 740, 1478, 1713} cautioned against relying on gold alone; chrysotherapy may be an important adjuvant but the patient should also be given the benefit of the general measures included in a conservative regimen. Cutts summarized the case for gold salts as follows: "Certainly their use is attended with real danger and even the best results are far from spectacular. In short, in the present stage of our knowledge there is no royal way to recovery from rheumatoid arthritis." Contrasting views were held on the one hand by Key⁹⁰⁴ who stated that chrysotherapy should be employed in "every case" of rheumatoid arthritis, and on the other hand by Short¹⁵⁹⁸ who concluded that "it carries a danger of toxicity too great for any but an indispensable drug."

Bismuth. In an attempt to find other metals as effective but less toxic than gold a few workers have employed bismuth. Various degrees of improvement were claimed for 60 per cent of patients with "arthritis" given sodium bismuth tartrate (Hall⁷⁴¹), but Douthwaite was not impressed with such treatment for

rheumatoid arthritis. Tarsy¹⁷⁷³ tried colloidal bismuth and colloidal platinum, metals with atomic weights approximately that of gold; results were essentially negative.

Fever Therapy. The recent trend has been to deprecate artificial fever therapy.^{554, 1856} Of 74 patients treated thereby (104° to 105° F. rectally for six sessions of three hours each; Kettering hypertherm), 44 per cent showed immediate improvement, but in only 18 per cent was it sustained after six months (Fetter and Schnabel). Osborne, Markson, Driscoll and Merriman submitted 27 patients to six or eight sessions of hyperpyrexia at 104° F. for four hours, induced by electromagnet. Improvement was marked in 22 per cent, moderate in 22 per cent, slight or none in 56 per cent; follow-up results were not reported. Concentrations of ascorbic acid in plasma were not changed notably by induced hyperpyrexia. Typhoid vaccine reactions were as effective as prolonged artificial fever.⁶³³ Prolonged fever induced with typhoid vaccine given by intravenous drip was again described.¹⁰²¹

Roentgen Therapy. Although results from roentgen therapy in rheumatoid spondylitis were encouraging, those in peripheral rheumatoid arthritis were so discouraging that Smyth, Freyberg and Peck abandoned such treatment. But others^{183, 990, 1754} reported "excellent results" when local irradiation (600 to 900 r) was applied to severely involved joints resistant to other measures; swelling often diminished; pain and soreness subsided; muscle spasm relaxed and mobility increased (if ankylosis was not present). Extravagant claims were made by Watt, who stated that "clinical cure" could be expected in 90 per cent of early cases, "arrest of further progress" in 80 per cent of moderately advanced cases, and "decrease of pain, more freedom of motion and arrest of further progress" in 70 per cent of advanced cases. Effusions of knees from "nonspecific synovial lesions" [rheumatoid arthritis?—Ed.] were eliminated from eight of nine joints treated by Horwitz and Dillman, but "asymptomatic synovial thickening" persisted in three joints. The same workers applied large doses of roentgen-rays (total doses as great as 8,000 r) to normal joints of dogs and on histopathologic examination found no evidence of articular damage resulting therefrom (dogs killed at varying intervals up to three and one-half months after exposure).

Radon. Local applications of radon ointment were considered useful,¹¹³⁴ but Kaplan⁹⁴⁶ condemned this remedy because it had little penetrating power, for radon is rapidly dissipated in air. Radon ointment proved "absolutely ineffective and useless for arthritic conditions"; to assume "it can influence the underlying joints or bones is entirely erroneous" (Kaplan⁹⁴⁶).

Rest and Motion. The importance of general physical and mental rest and rest for involved joints was stressed.^{46, 567, 1082, 1671} Simple rest is hard to enforce especially when patients begin to "feel a little better," but the physician must be firm to prevent reactivation and fatigue at any cost (Markson). Pemberton^{1364, 1365, 1371} stated that rest as a form of therapy is neglected by physicians; a survey showed that less than 11 per cent prescribed it. Most writers agreed that complete rest in bed was indicated only in severe, acute or febrile cases^{606, 739, 784} and during flare-ups with local heat and severe pain.⁸⁶⁰ But Stevens¹⁷¹⁸ took an extreme view and advised complete rest in bed "until all clinical and laboratory signs of activity have subsided, even in long-standing chronic cases." [Such advice is unrealistic and may be dangerous unless exercises and special care are used to prevent deformities.—Ed.] In chronic cases the minimal amount of rest should be 10 hours at night and two periods of one hour each during the day.^{418, 1487} During such periods affected joints should be placed in the best position to insure maximal function should deformity develop.¹⁶²⁹ Opti-

mal positions were described.¹⁰⁷¹ Daily systematic passive and active exercises to prevent joint stiffness and muscle atrophy are of utmost importance^{606, 626}; during the more active stages these should be gentle and nonweight bearing.

Physical Therapy. Many general articles appeared.^{07, 230, 295, 400, 411, 627, 601, 859, 880, 927, 1029, 1030, 1036, 1201, 1245, 1250, 1299, 1367, 1389, 1300, 1409, 1554, 1882, 1023, 1018, 1010} The value of home physical therapy by simple means (radiant heat, contrast baths and douches, wet packs, paraffin baths, hot tub baths, and others) was stressed.^{606, 1372}

Proper use of heat, massage, passive and active exercises can be taught to the patient or his family; home physical therapy is something which can be used every day of the year.^{395, 926, 1487, 1650} An electric pad or cheap heat lamp used consistently is of more value than elaborate machinery which is only occasionally available.¹¹⁵⁷ Treusch and Krusen made a follow-up study on 218 patients with arthritis for whom home physical therapy was prescribed. Of these 93 per cent carried out the prescribed treatments at home; 65 per cent continued the treatments for three months or longer. Two thirds (66 per cent) appeared to be benefited thereby. Treatments were more likely to be carried out and results were better when more than one period of instruction had been given; rheumatoid arthritics constituted the most diligent group. Cope-
man³⁷⁶ improvised methods of applying physical therapy in a military field hospital: sweat baths with a makeshift cabinet covered with blankets and the steam provided by boiling water in a five gallon can; a hot air bath made with two cradles covered with blankets and connected by a length of piping to a primus stove; radiant heat lamp improvised from petrol cans.

The physiologic effects of local heat differ but little whether they are conductive (electric pad, hot packs, hot water bottle), convective (infra-red lamps, bakers) or conversive (diathermy), except that the first produces the least penetration and the last the greatest.^{1036, 1388} Light massage over muscles with the stroke directed to help the return flow of venous blood aids in circulation and relaxation,¹⁶⁴⁹ but joints themselves should not be rubbed¹⁶⁴³; "there is no place in inflamed tissues for the use of ploughing, pounding and punching methods which only increase inflammation" (Ober¹³¹⁰). Massage does not increase muscular strength; this can be brought about only by active exercises.¹³⁸⁸ In general, exercises of joints should be begun as soon as any degree of painless motion is possible.⁶²² For an acutely swollen painful joint exercises should be delayed, but to wait too long favors development of permanent disability.¹⁶⁷¹ Exercises must be supervised and graduated¹¹⁵⁷; "purposeless wiggling of joints" should be condemned (Slocumb and Polley¹⁶²⁹). Exercises should not be done too enthusiastically, and if increased pain persists for more than two hours thereafter, the exercise has been too vigorous.^{593, 1187} Salicylates beforehand may aid in accomplishing joint movement. The value of underwater exercises, especially in a Hubbard tank, was pointed out.^{860, 1082, 1655} Solomon¹⁶⁷¹ outlined a useful set of simple joint exercises and a simple exerciser for knees was described (Newman). Electrical muscle stimulation is a "lazy man's way of exercising" (Osgood) and has little place in the treatment of rheumatoid arthritis, but active muscle training, such as muscle-setting and resistant exercises, is of great importance and should be begun early.⁷⁶⁷

Occupational Therapy. Discussions on the aims and importance of occupational therapy appeared.^{81, 771, 800, 988, 1092, 1149, 1329, 1343, 1459, 1529, 1541}

Occupational therapy is concerned mainly with the restoration of joint motion and muscle strength; it provides the patient with something constructive or useful to do, thereby ridding him of a feeling of helplessness and dependency.^{160, 261} Movements involving extension rather than flexion should be encouraged.⁵⁶⁹ Hurt gave the following principles for muscle building: for a poor muscle, exercise with gravity

eliminated; for a fair muscle, exercise against gravity or its equivalent; for a good muscle, exercise against gravity and graded resistance. Various measures and equipments were described.^{204, 306}

Spa Therapy. Several general articles described spas and their facilities.^{1005, 1670} The chief advantage of a spa is that it removes the patient from his everyday work and worry and places him in an environment of rest and recreation.¹⁰³² To stay at one of the "watering places" twice a year may be of some help,¹⁶⁴³ but patients in active stages of rheumatoid arthritis do better at home or in a hospital.³⁵⁹ The Medical Advisory Committee for Chronic Rheumatic Diseases (Scotland)¹²¹⁵ concluded that mineral waters possess no antirheumatic properties and that the therapeutic effects of spas are due to extraneous and accessory factors, not to the inherent qualities of the waters. According to Markson, "the health resorts have lost most of their reputation due to shady methods, absurd claims to healing virtue and the frequent presence of shady medical direction."

Climate. Many patients with rheumatoid arthritis receive symptomatic benefit from a constant, warm dry climate,¹²⁸⁸ but in the experience of Cecil³⁰⁵ those who respond most conspicuously relapse sooner or later when they return to their usual climatic environment. Although some doubt the importance of climatic influence, the fact remains that rheumatoid arthritis is rare in the tropics and diminishes in incidence toward the south¹¹⁵⁷; if the ugly northern winters can be avoided so much the better, but it is hardly practical in most cases to urge a patient to disrupt his livelihood to move to a warmer climate. According to Hill and Holbrook a warm, dry climate is helpful and for some patients "specific." Patients who had failed to improve on a conservative regimen improved on the same program after moving to southern Arizona. Seven patients with severe rheumatoid arthritis were kept by Edstrom^{509, 510} in "tropic chambers" with the air in the room at a constant temperature of 32° C. and a humidity of 35 to 40 per cent, a relatively warm but dry tropical atmosphere. Four patients became free of symptoms and capable of working; three (including one with Still's disease) improved temporarily but had relapses when treatment was stopped. Improvement was attributed to bettered peripheral circulation and increased relative oxygen saturation of venous blood.

Psychotherapy. Psychotherapy often serves as an important adjunct to more realistic therapy. To prevent attitudes of dependency, helplessness, frustration and self-pity the patient needs: (1) restoration of self-reliance; (2) development of a reasonably optimistic view as to prognosis; (3) avoidance of quackery; (4) persistence in carrying out standard methods of treatment; (5) financial help in some cases; and (6) occupational rehabilitation (Hench⁸¹³). Swaim^{1751, 1752} added to these a "regime of spiritual training." In his experience anxiety and resentment are the two most constant emotional reactions of arthritic patients, which suggest that maladjusted human relationships are a fundamental problem. Sometimes the patient, often the whole family, needs a change of heart, a new spirit of cooperation and interest.

The natural clinical course of the disease often fluctuates with the mental state. Halliday⁷⁴⁷ repeatedly noted the ameliorating influence of a new interest added to a cramping life situation, "giving the patient something to live for." Functional symptoms may be superimposed on those from the arthritis; pain may be disproportionate to the activity and extent of the disease (Short and Bauer¹⁶⁹¹). The physician should

discover and eliminate those fears and conflicts responsible for a low threshold of sensitivity. Perhaps the benefits from most forms of current treatment result from psychic effects (Davis ⁴⁴⁸). In one series significant improvement resulted in 40 per cent of patients given injections of sterile saline (Wetherby ¹⁰¹⁵). According to Markson ¹¹⁵⁷ "anything short of that which smacks of down and out quackery" may be instituted for discouraged patients rather than allow them to discontinue treatment entirely. [We would add: provided that (1) it doesn't cost the patient too much and (2) the physician doesn't "kid" himself. The psychotherapy is meant for the patient, not the physician.—Ed.]

Nonsurgical Orthopedic Measures. Such measures are aimed at keeping joints as free from pain as possible, at preventing flexion deformities and at maintaining normal motion.^{523, 1650} Simple plaster splints aid greatly in preventing deformities and should be employed early while medical measures are being instituted. During acutely painful stages plaster molds are indispensable but must be removed at least once daily to allow motion.^{116, 784, 1750, 1754} Warning was given against prolonged splinting to the point of marked atrophy of muscle and bone.^{1601, 1644} For flexion contractures "coaxing methods," not brute force, should be used.⁵⁷⁶ Flexion contractures of knees can often be corrected by a series of posterior plaster shells^{360, 561}; traction and manipulation, wedging casts and forceful stretching are ineffective [sometimes—Ed.] and often harmful.¹⁰⁴³ Special splints for correction of deformities of various joints were described.^{102, 164, 926, 1750, 1800}

Surgical Orthopedic Procedures. Kuhns and Dickson ¹⁰¹³ reviewed the indications for surgical procedures to correct flexion contractures of knees: manipulation under anesthesia for mild deformities due to capsular contractures without serious joint damage; posterior capsulotomy for resistant flexion contracture with little destruction of articular surfaces; osteotomy for fixations in bad position for weight-bearing and with extensive destruction of joint surfaces; arthroplasty for joints with bony ankylosis; arthrodesis for severely destroyed joints with persistent pain on weight-bearing in patients who must stand at work and for whom stability is more important than movement. Treating contracted knees, Kuhns ¹⁰¹³ obtained good results from posterior capsulotomy in 40 per cent of cases, from osteotomy in 33 per cent, from arthroplasty in only 10 per cent. Synovectomy was sometimes done for persistently swollen boggy knees without extensive articular destruction.^{369, 561, 1344} Excellent results were obtained in 50 per cent, definite improvement in 20 per cent, of 64 cases in which synovectomy was performed by Dickson. Less promising results were reported by Ghormley and Cameron; excellent results were obtained in only 16 per cent, some improvement in 41 per cent, poor results in 40 per cent of cases; at the time of review the remaining 3 per cent had died. This procedure can be done while the disease is still active (Key ⁹⁰⁴), but arthroplasty should not be done until the disease has become quiescent.^{756, 793, 992, 994} Arthrotomy and joint lavage were recommended by two British authors (Bastow ⁸⁵; Fischer ⁵⁶¹). Techniques for posterior capsulotomy were outlined.^{1410, 1445} Total excision of the patella in four cases (combined with synovectomy in three and with posterior capsulotomy in one) gave notable relief of pain in three.¹⁰⁸¹ Vitallium cup arthroplasty for persistently painful hips was discussed.^{180, 926, 1680} Results in 10 cases reported from the Mayo Clinic were: "very good" in 40, "good" in 10, fair or poor in 50 per cent.¹³⁰

Surgical procedures for correction of deformities of joints of upper extremity were described.^{408, 793, 994, 1522, 1614} Smith-Petersen, Aufranc and Larson ¹⁶⁴⁴ condemned such statements as: "wait until the acute condition quiets down"; "don't operate during the acute stage." They advocated earlier surgical intervention and de-

scribed such procedures as acromioplasty to relieve pain from associated secondary subacromial bursitis; excision of radial head for deformities of elbow; arthrodesis with excision of the distal end of the ulna for deformed wrists. Hass⁷⁹³ reported good results from arthroplasty of the elbow with restoration of motion in eight (53 per cent) of 15 cases. Arthroplasty for small joints of hands and feet, with tantalum between the joint surfaces, was reported.⁴⁰⁸ A patient with bilateral ankylosis of temporomandibular joints obtained an excellent functional result from excision of the heads of condyles.⁴⁷⁰ On one side a graft of muscle and temporal fascia was used to fill the defect; on the other side no graft was used; resulting function on the two sides was the same.

Sympathectomy. Lumbar sympathectomy does not affect the course of rheumatoid arthritis (Key⁹⁹⁴). In dogs the increased blood flow which follows sympathectomy gradually becomes reduced after nine or 10 years to approximately that of the control or innervated side. This is due to hypertrophy of the muscular coat of the arteries on the denervated side.⁵³⁷

PROGNOSIS IN RHEUMATOID ARTHRITIS

Regardless of the treatment used, Cutts found that 59 per cent of private patients and 53 per cent of clinic patients tended to improve definitely. About a fourth showed marked improvement approaching a cure; half showed slight or moderate improvement; a fourth failed to improve or were worse. Cecil wrote³⁰⁵: "Certainly a considerable number of patients with rheumatoid arthritis have remissions during which they are free of pain and swelling in the joints. These remissions are likely to come fairly early in the course of the disease and sometimes last for several years. Patients who have had rheumatoid arthritis for five to six years rarely get natural remissions. When the disease becomes inactive at this late stage, it seems quite natural to assume that it results from some particular form of therapy."

SO-CALLED INFECTIVE ARTHRITIS

Some writers^{567, 1392, 1596} distinguished between rheumatoid arthritis and the acute polyarthritis which follows in close temporal relationship to the development of an obvious focus of infection (sometimes called "focal infection arthritis," "postinfectious arthritis" or "infective arthritis"). In such cases articular involvement tends to be asymmetrical; large rather than small joints are predominantly affected; there is little or no tendency to progression; a chill and fever (102 to 104° F.) may occur at the onset; the sedimentation rate is markedly elevated and polymorphonuclear leukocytosis is present; the disease is self-limiting; the prognosis is better than in rheumatoid arthritis. [Five of us believe that this is just a variety of acute or subacute febrile rheumatoid arthritis; others of us do not agree.—Ed.] Pilot¹³⁹² concluded that hemolytic streptococci usually can be found in the focus and that whereas removal of tonsils and diseased teeth are of "little value in rheumatoid arthritis," a marked and often dramatic therapeutic response usually occurs in "focal infection arthritis."

STILL'S DISEASE AND FELTY'S SYNDROME

The literature on Still's disease (juvenile rheumatoid arthritis with splenomegaly, lymphadenopathy and anemia) was reviewed by Angevine who reported

six cases. Objective manifestations and the histopathologic findings in joints are identical with those in adult rheumatoid arthritis. Deformities appear earlier; demineralization occurs more rapidly and is usually more extensive; crippling and muscular wasting is greater as a rule; subcutaneous nodules are rare. But nodules were described by Field⁵⁵⁶ in one case. Eleven other cases of Still's disease were reported^{43, 410, 1368, 1808}; in one case Still's disease of three years' duration was complicated by diffuse amyloidosis. The original article on Still's disease, "On a form of chronic joint disease in children," was reprinted as a memorial to the late George F. Still.¹⁷²⁷ Some^{1704, 1700, 1767} would discard the term "Felty's syndrome," because it does not indicate a specific entity but rather a rare type of rheumatoid arthritis in adults associated with splenomegaly and neutropenia. Additional findings at times were hepatomegaly, lymphadenopathy, tachycardia, anemia, fever, cutaneous pigmentation, eosinophilia and monocytosis.^{701, 1117} The cause of the leukopenia and anemia remains uncertain. According to Steinberg¹⁷⁰¹ they are not due to depression of bone marrow: in two of his three cases the sternal marrow was studied and hyperplastic bone marrow with marked erythropoiesis and myelopoiesis was found. This type of marrow was considered identical with that in rheumatoid arthritis.

Although splenectomy has been advised for "Felty's syndrome," in no patient so treated have the beneficial effects on the anemia and leukopenia been more than transient; the postoperative course usually has been characterized by general decline (Hatch⁷⁰⁴; Waitzkin). [Decline and death a few months after splenectomy have been reported in several cases.—Ed.]

OSTEOARTHRITIS: DEGENERATIVE JOINT DISEASE

Following the British nomenclature adopted by the American Rheumatism Association, most writers now refer to "osteoarthritis" rather than "hypertrophic arthritis." Short and Bauer¹⁶⁰⁰ preferred the term "degenerative joint disease" because it does not imply the presence of inflammation and spares patients the fearsome term "arthritis." For the same reason Neligan preferred the term "arthrose." But some of the pathologic changes in osteoarthritis "meet the criteria of a chronic inflammation" (William Bauer⁹⁶; Goldberg⁶⁶²).

The clinical distinctions between primary and secondary osteoarthritis were upheld,^{1441, 1600} but both types give the same roentgenographic and pathological picture in affected hips.⁷⁶¹

PRIMARY OSTEOARTHRITIS (HYPERTROPHIC, SENESCENT, DEGENERATIVE ARTHRITIS)

Incidence. Degenerative joint disease is the most common articular disorder.¹⁰⁰⁸ All persons beyond the second or third decade of life exhibit degenerative changes in joints,^{721, 1600} but skeletal symptoms rarely occur before the age of 40 years.^{968, 1010} According to Howell "rheumatism" is not an inevitability of old age: among 400 males more than 65 years of age only 35 had symptoms of "rheumatism," of which only six had osteoarthritis sufficient to require treatment; fibrositis was more common. Due to the preponderance of younger men in the army, only 7.5 per cent of the rheumatic patients admitted to an army general hospital in 1942 had osteoarthritis (Boland).

Special Clinical Features. Pain in the arm with paresthesias in fingers from cervical osteoarthritis was again described (Kelly⁸⁷⁰). Pain in a shoulder from osteoarthritis of acromioclavicular joint was relieved by roentgen therapy (Openheimer¹³²⁰). A synovial cyst of the skin (a rather rare lesion which may accompany Heberden's nodes), after injection of a contrast medium, was found by roentgenograms to be connected with the joint cavity. Hence Eliassow and Frank concluded that such synovial lesions of skin are "due to an escape of synovial fluid from the joint cavity." Acroparesthesia commonly accompanies Heberden's nodes.²³⁵⁰

More attention is being paid to osteoarthritis of temporomandibular joints.^{96, 289, 1203, 1558, 1588, 1600, 1848, 1931} Short and Bauer¹⁶⁰⁰ listed the many symptoms which may result from osteoarthritis of this joint (symptoms sometimes referred to as "Costen's syndrome"). These include deafness, tinnitus, earache, dizziness, nystagmus, headache, herpes of the external auditory canal and buccal mucosa, and burning or dryness of mouth or tongue. Erosion of the bony portions of this joint have been thought to affect hearing but Shapiro and Truex could not prove this. About 100 rice bodies were removed from an osteoarthritic temporomandibular joint.²³⁹

Pathology. Pathologic studies of surgical and necropsy material indicated to Goldberg⁶⁰³ that cartilage erosions occur simultaneously on both opposing surfaces of an articulation rather than erosion on one surface being accompanied by corresponding overgrowth on the opposing surface as has been taught. Magnuson described two forms of cartilaginous degeneration: one starts at the surface and progresses toward the matrix, the other starts at the matrix and progresses toward the surface. In the first type, surgical removal of the degenerated tissue was followed by hyaline regeneration provided the process had not extended through the whole thickness of cartilage; in the second, hyaline regeneration did not occur but the defect was filled by fibrocartilage which seems to serve as an adequate covering to prevent friction. In articular cartilage of cattle a definite progressive diminution of cellular density occurs with age.¹⁸⁶⁹ Impairment of oxidative activity of old cartilage cells was noted also and suggested that the changes incident to age result from the inability of the numerically reduced cells to "breathe" properly.

Laboratory Data. Liver function, measured by the hippuric acid test was subnormal in five of 15 cases.⁸²³

Etiology and Pathogenesis. 1. *Factor of Trauma.* Confirmation of the generally accepted idea that long-continued minor trauma is the most important etiologic factor¹⁸⁹² was found in Magnuson's work on dogs.

Various types of gross damage to cartilage, injections of irritating chemicals and bacterial toxins, and introduction of foreign bodies failed to produce proliferation of bone or degeneration of cartilage in regions other than those immediately involved. Typical degenerative arthritis was produced experimentally only one way: by allowing the animal to subject the joint to oft-repeated slight trauma. This was done by cutting medial and crucial ligaments to render joints unstable and then allowing the dogs to run freely. Typical exostoses formed in six to nine months and appeared before significant degeneration of cartilage was noted. Magnuson concluded that human degenerative arthritis probably results likewise from repeated small trauma. "It may be aggravated by low-grade infection or chemical or metabolic toxemia. Once roughening is established, the mechanical irritation of this roughening is sufficient for

prolongation of symptoms and disability." [Excellent colored photographs accompanied Magnuson's article.—Ed.]

2. *Factor of Heredity.* A familial tendency for the development of Heberden's nodes was statistically demonstrated by Stecher and Hersh.^{1093, 1094}

Among 68 families of patients with Heberden's nodes the mothers of such patients were similarly affected twice as often, the sisters three times as often as the general female population. The incidence of Heberden's nodes in the general population was as follows: in females 2.6 per cent at the sixth decade (50 to 59 years of age) increasing to nearly 30 per cent in the ninth decade; in males from 3.6 per cent in the sixth decade to 8.4 per cent in the eighth. Through all age groups the sex ratio is 10:1. Despite an apparent lack of agreement with mendelian ratios, the data suggested that the genetic mechanism involved a single autosomal gene, sex influenced, dominant in females, recessive in males. This conclusion is not now directly applicable to other forms of osteoarthritis.

3. *Factor of Impaired Circulation.* Of 71 osteoarthritic patients 23 (32 per cent) presented arterial spasms, but only 32 per cent of 86 "controls" (patients with advanced organic arterial disease) had evidence of "rheumatic or arthritic involvement" (Steinbrocker and Samuels¹⁷⁰⁸). "Pronounced arterial disease alone does not usually produce arthritic signs and symptoms."

4. *Factor of Neuroendocrine Dysfunction.* Pemberton and Scull^{1361, 1370, 1371, 1372, 1373} consider both osteoarthritis and rheumatoid arthritis basically metabolic disorders due to an "imbalance of the neuroendocrine system" which "involves several links of the system rather than a single outstanding dislocation."

5. *Factor of Gastrointestinal Dysfunction.* Roentgenographic abnormalities of gastrointestinal tract, especially in colon, were found by Pemberton more often in cases of osteoarthritis than in rheumatoid arthritis. No one abnormality was characteristic. It was not determined whether they are the cause of, or the result of, the arthritis.

[They may not be either; they may be coincidental.—Ed.]

6. *Factor of Infection.* Almost as many infected foci were found by Bach⁴⁰ in 77 cases of osteoarthritis (total 276 infected foci; average 3.5 for each patient) as in 99 cases of rheumatoid arthritis (total 428 infected foci; average 4.3 for each patient). Regardless of their etiologic rôle Bach⁴⁰ believed they should be eradicated even in osteoarthritic patients.

Medical Treatment. For osteoarthritis the expression "active medical treatment" is less appropriate than "management" since unfortunately treatment is limited in scope and value and no new remedies of proved worth have appeared. "The obvious thing to do is to 'spare' the joints, just as one spares a horse that is 'a bit gone in the forelegs' or a car with a worn transmission." So wrote Neligan. "If the patient will cooperate, the wearing of his joint may be stopped; it will at any rate be slowed down." The usual measures were recommended: reassurance; rest periods; reduction of traumatizing excess weight; heat.^{820, 1042} Of 158 patients with disabling osteoarthritic hips 30 per cent were "entirely relieved," 37 per cent greatly improved by various treatments, especially roentgen therapy or manipulations (Kuhns¹⁰⁴²). Patients with osteoarthritic hips or knees should avoid living in hilly districts; those with affected hips who insist on hunting or riding "should get a pony with a small barrel."¹²⁹²

Currently physicians seem to have an urge to make intra-articular injections into hips or knees with "good" results in the usual 60 to 80 per cent of cases

regardless of what was injected. Thus injections of 1 per cent acid potassium phosphate gave "lasting benefit" to 60 per cent of Crowe's⁴¹² patients, and "temporary relief to all others." By "acidifying the joints" with injections of lactic acid of pH 5.8 Waugh again claimed relief in 70 per cent of patients so treated. Injections of 10 per cent benzyl salicylate improved 80 per cent of Elkin's⁵¹⁷ patients. Testosterone propionate presumably was of value in two of three cases of osteoarthritis in males.⁷¹⁶ Thyroid and estrogenic hormones were considered useful by a few.³²⁴

[Until these results have been confirmed we do not recommend such treatment.—Ed.]

Roentgen therapy to control pain^{970, 1042, 1320, 1887} or mecholyl iontophoresis⁷⁷⁹ were again recommended. A bedtime dose of quinine sulfate (3 grains; 0.2 gm.) will relieve night cramps in calf muscles, which occur so often in patients with osteoarthritic knees (Gootneck).

Surgical Treatment. Removal of loose bodies from osteoarthritic knees may be necessary to overcome mechanical locking (Colonna). Manipulation under anesthesia was used in selected cases.^{820, 1042} Synovectomy, only rarely indicated, gives good results in selected cases (Ghormley and Cameron). Cheilotomy, simple excision of osteophytic fringes of long spurs around acetabular margin or femoral head, may be a useful, though often temporary, expedient.³⁶⁰ Arthrodesis is the surest way to relieve painful hips,^{639, 733} but few patients are willing to accept an ankylosed hip. In selected cases excellent results with resultant movable joints may be obtained from cup arthroplasty.^{139, 639, 763, 766}

Recently reported were results from cup arthroplasty obtained by Bickel, Ghormley, Coventry and Mussey in 27 cases of osteoarthritis of hips, sometimes of the primary (idiopathic, senile) type but generally of the type secondary to congenital anomalies, Legg-Perthes' disease and so forth. Results eight months to five years after operation were as follows: in 15 per cent results were "very good": the patient was able to walk without support and had good motion of the hip with no noticeable limp or pain. In 30 per cent results were "good"; pain was absent or minimal; the patient could walk well on the level and on stairs, although at times a cane was required. In the remaining 55 per cent results were only fair or poor. Results were better among men than among women. Cup arthroplasty was recommended by Ghormley,⁶³⁹ not for hips that are merely painful, but in cases in which much limitation of motion is also present. It was not recommended for patients more than 60 years of age.

Cup arthroplasty was done by Harmon^{763, 766} on 16 hips of 13 patients. Results 18 months later follow: "excellent" in 10 hips (62 per cent); "good" in three (19 per cent); poor in three (19 per cent).

Although hips or knees were joints usually so treated, a satisfactory tantalum cup arthroplasty of a first metatarsophalangeal joint in a wounded marine was reported (Crosby and Galasinski). Harmon⁷⁶³ treated metacarpophalangeal and temporomandibular joints with small plastic cups with excellent results "in all cases." [Numbers not stated.—Ed.]

Vitallium cups, superior to lucite cups, were generally used.^{139, 642, 1680, 1804} But Harmon⁷⁶³ preferred cups of methacrylate plastic which permit postoperative roentgenographic visualization of joints.

Apropos of the introduction of metal (cups or nails) into joints Neligan asked: "Does metal in a hip joint contraindicate the use of diathermy?" A patient whose fractured hip with traumatic osteoarthritis was treated by nailing was, a year later,

"convinced that she had had very much more pain after she had had a few (diathermy) treatments."

[According to Dr. Frank Krusen, physiatrists apply diathermy with caution or not at all to a region containing implanted surgical metals. Recent studies by Pudenz, Gersh and Etter indicate the comparative safety of the procedure, at least when the metal is implanted in tissues having a normal supply of blood. But Krusen agreed with Lion (1947) that diathermy should always be applied with caution over regions containing implanted surgical metals.—Ed.]

Postoperative exercises are a principal factor in results obtained from reconstruction operations (Preston¹⁴⁰⁹).

Patellectomy, recommended for osteoarthritis of knees by Tippet (1938) and Berkheiser (1939), was done by Young and Regan¹⁰⁸¹ when painful motion (even without weight-bearing) was presumably due to a mechanical impediment to function. Total patellectomy, sometimes bilateral (with or without cheilotomy), was done in 14 cases of osteoarthritis: results were excellent in seven, good in four, fair or poor in three. In nine cases pain was relieved completely. The operation "permits a good range of motion, diminution of pain and a surprisingly stable knee" (Colonna). Opinions differ as to the relative functional importance of the patella.¹⁰⁸¹ Although the patella is being removed to help osteoarthritic patients, experimental tibiofemoral osteoarthritis can be produced in rabbits by total patellectomy.³⁵⁴ [Indications for total patellectomy have not, in our opinion, been clearly defined, nor can final conclusions on its value be determined from the few cases reported to date.—Ed.]

SECONDARY OSTEOARTHRITIS

The causes of secondary osteoarthritis of hips were listed by Ghormley⁶³⁹ and Harmon.⁷⁰³

They included: (1) for juveniles and adolescents, coxa plana (Legg-Calve-Perthes' disease); slipped upper femoral epiphysis; septic arthritis (with or without dislocation); childhood arthritis (Still's disease); congenital dislocation; congenital aplasia of acetabulum; congenital anomalies of upper part of femur; coxa vara of other types (rickets, osteomalacia); (2) for adults, injury followed by aseptic necrosis of femoral head; fracture of pelvis into acetabulum; fractures of femoral neck; traumatic dislocation complicated by late avascular necrosis; rheumatoid arthritis; septic (suppurative) arthritis; protrusio acetabuli (Otto pelvis) traumatic or infectious in origin; Paget's disease of pelvis and upper part of femur; Caisson disease; chondromatosis; osteochondritis dissecans; syphilis (painless "Charcot's hips").

(For other data on secondary osteoarthritis see the section on "Diseases of Joints Related to Trauma.")

BACKACHE AND SCIATICA

More than 500 papers on backache appeared during the period under review; many described proper methods for taking histories, special physical examinations and roentgenographic studies of patients with backache.^{203, 418, 453, 620, 610, 641, 851, 904, 913, 1214, 1284, 1088, 1729, 1750, 1932, 1945, 1970, 1984, 1990}

Backache from Lumbrosacral and Sacroiliac Sprains and Strains and from Sacroiliac Subluxations. No new, precise criteria were described for the diagnosis of these vague conditions.^{48, 208, 364, 929, 930, 931, 1211, 1258, 1265, 1415, 1871, 1994}

Symptoms which indicated lumbosacral or sacroiliac sprains or sacroiliac subluxations to some writers seemed much like those set forth by others as symptoms of protruded disks.

Flexion-strains of spines of cadavers applied by a screw machine produced rupture first of intertransverse ligament and quadratus lumborum fascia, then of annulus fibrosis and adjacent ligaments, and finally of supraspinal ligaments and intervertebral disks.⁷²³ Strains due to "imbalance between the capacity of structures of the back, and the physiologic demands made upon them" were again blamed for most low back pain.

Treatment of back strains should be the same as that of muscular or ligamentous tears elsewhere in the body: the injured structure is placed in a position of relaxation (by rest in bed, physical therapy, plaster shells, back supports) until healing is at least partially completed (Kuhns¹⁰⁴¹). Local injections of anesthetics and manipulations were recommended for acute strains.^{38, 565, 929, 930, 931, 1003}

Industrial Backache. Backaches in industrial workers, "the bane of the industrial medical practitioner," are often characterized by disability greatly out of proportion to physical findings.⁹⁷³ Compensation factors confuse the picture.⁶⁵

The high incidence of this condition was shown by the fact that in one steel plant in one year there were 190 claims among 3,700 workers.¹²¹⁴ To reduce such claims other workers were instructed how to lift heavy objects; the result was that during 10 years an average of only five weeks yearly was lost by a group of 2,200 workers.¹²⁸⁰

Gradual physical rehabilitation effectively reduced time lost from work because of back injuries.^{479, 922} Patients were first given light work, then gradually returned to former occupations. Thus 92 per cent of persons with "acute industrial backs" returned to work within five days. Industrial workers with compensable back injuries involving protrusion of disks or hypertrophy of ligamenta flava had excellent results from surgery and returned to work as early as did nonindustrial workers.⁵⁰²

Postural Backache. A few writers discussed lame backs caused by faulty posture.^{265, 641, 1072, 1114, 1795, 1993} In this condition backache develops after standing or hard work, is relieved by rest, and does not interfere with sleep. The patient is free from pain in the morning on arising. It is a fatigue phenomenon. Treatment includes postural exercises, regulated rest, physical therapy and supports.^{285, 1255, 1258, 1795, 1984, 1993} The patient's understanding and cooperation are essential; he must devote much time and effort to overcoming his defect and can obtain good results only if he is willing to use graduated exercises for a long time.⁶⁴¹

Backache from Tight Fascial Bands. Fasciotomy of iliotibial band was again recommended for the relief of contractures.^{1309, 1311, 1387, 1945} Of 86 patients so treated 41 had excellent results, 33 were improved, 10 were not significantly improved. Conservative measures, often successful, should be used before surgery is undertaken.¹³⁰⁹

Another form of fasciotomy was recommended: subperiosteal stripping of ligaments, muscles and fascia from their attachments to the posterosuperior spine of ilium and posterior third of the iliac crest (Heyman). Certain patients with backache "unrelieved by usual orthopedic measures" were treated with either or both these types of fasciotomy which were regarded as supplements to conservative therapy.⁷³⁶

Backache from Spondylolisthesis. Among Meyerding's^{1233, 1234} 745 patients with spondylolisthesis were 80 (10.7 per cent) with backache and also sciatica. The latter presumably was caused by a prolapsed disk as was proved by operation in six cases (removal of disk and spinal fusion).^{1233, 1234} All symptoms associated with spondylolisthesis were attributed by Dandy⁴³⁰ to "defective intervertebral disks." "The end

result of removal of disks was fusion of the opposing vertebrae and stabilization of the spine"; bone grafts were unnecessary.

Spondylolisthesis is generally developmental but may result from injury. Three traumatic cases were noted: vertebrae with the laminar defects were not displaced as is usual in developmental cases; slipping took place at the body below the defect (Kleinberg and Burman).

Backache from Reverse Spondylolisthesis. No new data appeared.

Backache and Sciatica from Primary Sciatic Neuritis. Fifty-five cases were reviewed²¹; most (67 per cent) were in males doing muscular work and exposed to changes in weather. The incidence was highest between the ages of 30 and 60 years. The condition, which was generally self-limited, lasted from one to 12 weeks, occasionally from a few months to five years. The distinction from secondary sciatica was based on finding of tenderness in nerve trunks and absence of abnormalities in spinal fluid. [We doubt the validity of this differentiation.—Ed.]

Backache with Osteoporosis. A study of 208 cases noted in the "Eighth Rheumatism Review" was reported in more detail.¹⁴⁵ Two new series were reported.^{203, 1201} Acute or chronic pain was present in some, absent in others. While some patients were performing trivial movements, agonizing, sometimes "nauseating" pain, appeared low in the back. Some heard a crack, snap or "give" in the back. Loss of height was sometimes notable. Principal signs were kyphosis or kyphoscoliosis. In some cases oblique folds of skin ran downward and outward in the thoracolumbar region and a deep transverse abdominal furrow was present. Roentgenologic changes included osteoporosis, biconcavity, collapse, wedging, crushing, localized fractures of vertebral bodies and pseudarthroses between lumbar spinous processes.

Necropsies in three cases disclosed extreme osteoporosis, attenuation of cartilage plates separating the disks from the bodies, squat biconcave vertebral bodies and bulging nuclei.

Treatment included dietary supplements of calcium and vitamin D, and orthopedic supports (plaster bed for night use, and corsets or a steel and leather support for day use). Patients improved clinically but not roentgenographically. Five or six years [sometimes more—Ed.] of such treatment may be required before [if ever—Ed.] the skeleton regains its former calcium content.²⁰³

Backache from Hypertrophied Ligamentum Flavum. According to most writers on this subject diseased ligaments sometimes cause sciatica with symptoms like those of protruded disks.^{572, 1260, 1334, 1425, 1976, 1977} Others disagreed.^{288, 803, 1415}

When only hypertrophic ligaments were found, results of surgery were generally poor.⁵⁷² Histologic evidence of disease in the ligaments included fibrosis and breakup of laminations of elastic fibers, and replacement by collagen fibers, presumably from degenerative changes.^{1096, 1210} The size and thickness of the ligamentum flavum seemed less important than histologic changes. Measurements were unreliable because of technical factors.

Backache from Metastatic Lesions. Features which permit diagnosis before roentgenographic evidence of metastasis appears were described.^{350, 1353, 1803, 1930} Pain may be segmental and aggravated by coughing, sneezing, yawning, straining at stool, bending or sudden jarring. It is constant, unmitigatingly intense and not influenced by climatic changes. The patient is often reluctant to move

or turn. Percussion tenderness is a constant sign. But some patients with extensive spinal metastatic lesions are free of pain.¹⁸⁰⁵ [Backache requiring narcotics results usually from metastatic malignant lesions.—Ed.]

Backache from Urologic Lesions. Of certain patients complaining of backache 79 per cent had prostatitis and seminal vesiculitis,¹¹⁷⁵ treatment of which relieved the majority. In 12 patients with hydronephrosis backache was the chief symptom.¹¹⁴⁸

Backache from Gynecologic Lesions. No new data appeared.

Backache from Gastrointestinal Lesions. Backache frequently results from diseases of the digestive organs.¹⁴⁶⁸ Penetrating gastrointestinal lesions caused acute, localizable pain, often limited to segmental distributions. Lesions in retroperitoneal tissues caused deep-seated pain which was severe and only fairly well localized. Metastatic spinal lesions produced boring, deep-seated constant and bilateral pain.

The Dorsolumbar Syndrome. This condition, also known as causalgic backache, was said to comprise a definite clinical entity in which pain occurs in lumbar muscles and extends along the twelfth rib.^{881, 1022} The term "causalgia" was used because the pain is of a burning type. The syndrome was reproduced experimentally by elevating one heel: after three weeks the subject noted pain characteristically extending around the side as in dorsolumbar syndrome. Change of position and exercises caused the symptoms to disappear in two weeks.

The disease results spontaneously from injury or irritation of the quadratus lumborum muscle; the resulting contraction deflects the last rib downward and forward and thus increases the distance that the twelfth thoracic nerve traverses from its foramen to the subcostal groove. This produces painful tension in nerve sheaths, to relieve which the patient assumes a position of scoliosis.

Backache from Adolescent Kyphosis. This condition was said to result from destruction of nucleus pulposus before ossification of the vertebral body is complete. When this occurs, the weight-bearing function is transferred to the bodies anteriorly, and the axis of motion to the posterior vertebral joints; spinal flexion produces increased pressure at the anterior borders of vertebral bodies. If the patient is adolescent and the epiphysis is subject to trauma, abnormal ossification follows, leading to premature closure of the epiphysis, failure of ossification of the anterior portion of the vertebral body and wedge formation. Later the wedge-shaped bodies develop spurs at their anterior angles. The degenerated disk may ossify and bridges may form between spurs. Patients with this condition characteristically are stooped, have prominent abdomens and protruding necks. There may be scoliosis (MacGowan).

Backache from Spasm of the Levator Ani, Coccygeus and Piriformis Muscles. These were described.¹⁰²⁴ Diagnosis was made by discovery of tenderness in the respective muscles on digital rectal palpation. Massage per rectum,¹⁰²⁴ infiltration of the first three sacral nerves with procaine,¹⁵⁸⁹ and section of the piriformis muscle⁵⁹⁶ were recommended.

Backache from Diseased Interspinous Ligaments or from Rickets. No data appeared.

Backache from Diseased Articular Facets. The inclination of sacral facets was found to average about 50 degrees from the sagittal plane: in 79 per cent of cases studied this did not vary more than 10 degrees; in 21 per cent the deviation was from 11 to 30 degrees. One out of five patients showed appreciable asymmetry associated with osteoarthritis (Badgley⁵⁰).

An anatomic study showed that lumbosacral facets suffer from all the ills inherent to joints: degeneration of articular surfaces; thinning and fibrillation of cartilage; osteophytic marginal proliferation; detached chondral bodies; even

complete loss of cartilage. True subluxations of apophyseal vertebral joints may occur if there is narrowing of the disk between the vertebrae. To be significant, dislocation of facets must be sufficient to produce impingement on the pedicle above and on the lamina below, thus causing backache. At such a site a protruded disk also may be present.⁵⁰

By injecting oil into the fourth and fifth lumbar apophyseal joints Larmon¹⁰⁶⁷ produced sufficient swelling to compress spinal nerves in the foramina: presumably arthritic swelling of these joints could similarly cause pain.

Technic for roentgenographic demonstration of lesions of facets was described.^{1505, 1506}

Backache from Fibrositis. This will be described under "Fibrositis."

Backache from Congenital Anomalies. Low back pain was more frequent among persons with congenital anomalies of the lower part of spine than among others.^{872, 1033} Some spinal anomalies strengthen the region; others decrease stability and predispose toward abnormally increased stress.

Psychogenic Backache. The general topic of psychogenic rheumatism is discussed later. Psychogenic backache has features which a history and physical examination will usually reveal and which permit accurate diagnosis, not just diagnosis by exclusion.

Symptoms complained of by patients with psychogenic backache were listed by Luck thus: (1) pain in coccyx extending up the spine to the thoracic region, neck or top of head; (2) pain not increased or relieved by any particular position; (3) pain not influenced by bending, lifting or lying down; (4) back pain not influenced or aggravated by rest or immobilization; (5) pain appearing near the coccyx or in wide areas of the back directly after healing of an organic low back lesion; (6) tingling and numbness in spine or extremities; (7) daily variations in the site of pain; (8) sensations as if part of the back were "missing" and "out of full control"; (9) feeling of a lump low in the back; (10) feeling of tension in the back that cannot be relieved; (11) constant throbbing in the back.

Although frequently absent, objective findings (when present) in cases of psychogenic backache may include (1) hysterical paralysis, (2) hypalgesia, (3) camptocormia, (4) diffuse tenderness, (5) vasomotor instability, (6) tachycardia, (7) apprehensiveness.¹¹³⁰ Backache from psychic disorders was ascribed to powerful muscular contractions during dreams in some cases (Saul). Overtreatment of trivial back injuries may exaggerate psychogenic backache. "The overly enthusiastic, talkative physical therapy technician suggesting a curvature of the spine here, a spasm in the muscle there, or the presence of painful nodes, is a menace in any back case" (Mock).

Psychogenic backache alone or aggravating organic diseases frequently affected soldiers during World War II (Boland and Corr). Such psychogenic disturbances interfered notably with recovery from organic types of backache. Successful treatment required the combined efforts of internists, physical therapists, orthopedists and psychiatrists. Treatment included postural exercises, use of charts and diagrams illustrating the dynamics of posture and supervised relaxing activities (Fox⁵⁵¹). [It also should include psychotherapy.—Ed.]

Backache and Sciatica from Osteitis Condensans Ilii. This disease produces a symmetrical sclerosis of the ilium adjacent to the lower portion of the sacroiliac joint. The patients suffer recurrent attacks of low back and pelvic pain, usually worse on one side than on the other. In eight of 23 cases, onset of symptoms occurred prior to or following delivery, and all the patients were women of childbearing age. The sedi-

mentation rate was normal in 21, elevated in two; other laboratory tests were negative. There was no tendency for the process to progress to involve the vertebral joints.⁷⁵⁵ [Could these cases represent localized rheumatoid sacroiliitis?—Ed.]

Miscellaneous Causes of Low Back Pain. The following conditions causing low back pain with or without sciatica were described: spinal epidural abscess^{185, 239, 240}; functional disorders of the foot; "nipping of soft tissues" between ribs and pelvis¹⁹⁹¹; backache of "reflex origin"⁸⁹³; functional decompensation of back⁷⁹⁸; backache due to downward subluxation of fifth lumbar vertebra on sacrum^{209, 210}; subarachnoid hemorrhage¹⁵⁴²; Paget's disease; hemangioma of vertebrae^{146, 551}; endocrine disorders.⁸⁹¹

BACKACHE AND SCIATICA FROM DISEASED INTERVERTEBRAL DISKS

Over 200 papers were reviewed; only a few can be mentioned.

The anatomy and pathology of intervertebral disks were studied.^{200, 308, 513, 894, 1257, 1265, 1321, 1323, 1421} The belief that expansile qualities are possessed by disks was considered erroneous.^{200, 474, 1470} Disks were said to be plastic but not expansile. [Others still insist they are expansile.—Ed.] The cushion-action of the disk is due to its passive distortion as a result of muscular action on spine, not to actual compression of the nucleus. Roberts¹⁴⁷⁰ regarded an essential tonus of the annulus as the pressure-producing agent, but Doel considered this impossible and attributed the compression to muscle tone, gravity and atmospheric pressure.

By analyzing the force vectors which result from lifting a weight of 50 pounds (22.7 kg.), it was estimated that pressure of 500 pounds (227 kg.) is exerted against the lower lumbar disks. When the spine is flexed, the nucleus pulposus migrates dorsally, tension is thrown on the posterior portion of the annulus, and the annulus may be subjected further to torsional stresses. These considerations were believed responsible for the high incidence of posterior protrusions of lumbar intervertebral disks.⁸⁹⁴

Acute Infectious Lesions of Intervertebral Disks. No new data appeared.

Calcification of Intervertebral Disks. In adults, especially the elderly, calcification of disks occasionally accompanies degenerative changes (Albert¹⁵); rarely it may be caused by ochronosis (Freund⁵⁹⁹; Hertzberg). In childhood the condition is rare, probably the result of infection; such a case was reported (Weens).

Spinal Puncture Injuries. Collapse of a disk with narrowing of intervertebral space and marginal proliferation sometimes follows injury by spinal puncture needles.^{481, 528, 540, 1504, 1722, 1742} Needles inserted into the subarachnoid space were studied roentgenographically and were frequently seen in a position where further insertion could have resulted in puncture of the annulus fibrosus and possible damage to the nucleus.¹²⁷²

Ruptured Intervertebral Disks. 1. Cervical Region. Ruptured fifth, sixth, seventh and eighth cervical disks produce characteristic syndromes of pain in the neck extending into certain regions of shoulder, precordium and hand. These syndromes were described.^{220, 248, 355, 439, 520, 1237, 1289, 1580, 1687, 1733} The picture may simulate that of coronary occlusion, scalenus anticus syndrome, cervical rib or brachial plexus neuritis.

Although the diagnosis of protruded cervical disks at times may be made without myelograms,⁵²⁹ opaque oil myelography was considered a valuable diagnostic adjunct. With care, the oil can be prevented from entering the cranial cavity. When some accidentally entered the skull, no untoward results occurred.

Protrusion of intervertebral disks may result from "recoil injuries" in which the

cervical part of the spinal cord is severely damaged without demonstrable or commensurate roentgenographic evidence of injury to the spinal column.⁴⁰⁴ Herniation of an ossified cervical nucleus pulposus caused complete transverse myelitis in one case.²¹⁷

2. Lumbar Region. Many new cases were reported. Usually symptoms of protruded lumbar disks result from pressure on nerve roots. When protrusions are massive, symptoms resembling those caused by compression of cord may result. This may readily be mistaken for tumor.^{445, 541, 508, 1852}

In one case a protruded lumbar disk produced complete spinal block (Froin's syndrome).⁸⁸² Four cases of maternal obstetrical paralysis and so-called neuritis of pregnancy or the puerperium with paralysis of one or both lower limbs were attributed to protruded disks.¹³¹³ Relaxation of pelvic ligaments during delivery may predispose to protrusion of a disk.

3. Diagnosis. Special neurologic tests and diagnostic maneuvers were described and illustrated.^{77, 192, 501, 088, 798, 1059, 1120, 1271, 1383, 1403, 1404, 1415, 1418, 1597, 1634, 1851} A new dermatome chart of lower extremities was useful in localizing protruded disks without the aid of myelograms. Keegan^{900, 901} prepared it by studying hypalgesia resulting from proved single lesions of nerve roots caused by protruded disks. The locations of dermatomes in this new chart differed from the classic patterns described in textbooks on anatomy.

Many negative explorations for suspected disks were attributed to "concealed disks."⁴²⁶ The disk bulges so slightly that it is not disclosed by iodized oil and can be found at operation only by careful inspection. Symptoms are like those of protruding disks. Pains were attributed to adhesions to the nerve, rather than to mechanical pressure. Proper treatment requires removal of disk.

Diagnosis of herniated disk as distinct from torn or degenerated disk was made by Young¹⁰⁸⁵ on a combination of signs which he called "the compression syndrome"; pain on standing flexion, pain on extension, pain on flexion to the sound side, and deformity either in forward flexion, or flexion to the sound side, or both. Characteristics of "nerve root pain" caused by protruded disks (or other diseases affecting sensory nerve roots) included (1) intensification on sudden increase in intra-abdominal and intrathoracic pressure, and (2) intensification by bending the head forward, stooping, straight leg raising, the Lasègue maneuver and spontaneous elongation of the spine during sleep (Eaton⁴⁹⁷).

The diagnostic value of contrast myelography with the use of air,^{8, 201, 453, 1050, 1431, 1548, 1663, 1904} oxygen,⁷⁵⁰ lipiodol,^{177, 520, 803, 1038, 1423, 1688, 1904} thorotrast,^{202, 253, 1301, 1300} and pantopaque were reviewed. The 500 oxygen myelograms studied by Hare and Langs⁷⁵⁰ were "85 per cent accurate." Although a positive finding in an air or oxygen myelogram was considered of diagnostic importance, the lesion could not be detected in all cases by this means. A normal, air or oxygen myelogram was not sufficient for ruling out a ruptured disk. Succeeding injections of lipiodol sometimes revealed pathologic processes. Headache, following air myelography, may be severe and incapacitating.

Advantages and disadvantages of thorotrast were discussed. An alkaline buffered suspension of thorium dioxide in a protective colloid, dextrin, was used. This has a low viscosity which permits almost complete removal from the subarachnoid space by forced spinal drainage. Its radioactivity is supposedly not sufficient to produce pathologic effects. Excellent contrast roentgenograms were obtained thereby but the time-consuming procedure of continuous spinal drainage necessary for its removal was a serious objection.¹⁰⁸⁵ It was considered dangerous by Bradford²⁰²: in one case signs of meningitis developed after its use.

Lipiodol was considered reasonably safe, but most writers agreed that lipiodol should be removed after roentgenograms are made. Technic for removal of lipiodol was described.⁹⁴² Its removal may be sometimes difficult and incomplete.

The new contrast medium, pantopaque, introduced by Steinhausen and colleagues, is a mixture of isomeric ethyl esters, the principal constituent of which is ethyl iodo-phenylundecylate. It casts an excellent shadow in roentgenograms but is not so opaque that it obscures fine gradations of density. Its use in diagnosis of protruded disks was described.^{36, 117, 386, 404, 408, 1409, 1555, 1678, 1688} It is absorbed slowly. (Lipiodol is not absorbable.) It is stable in solution, not miscible with spinal fluid and is nontoxic. All but a few drops can be removed and in most patients in whom it was allowed to remain no ill effects were suffered. But Schnitker and Booth noted three patients among 100 studied with this agent, in whom symptoms of meningismus with elevation of cell count and total protein of spinal fluid resulted.

False-positive contrast myelograms may result from (1) bulging of the entire disk without herniation, (2) backward and downward settling of a vertebra due to degeneration of a disk with narrowing of interspace, or (3) forward projection of the ligamentum flavum because of proliferation of margins of underlying facets (Horwitz). These may cause discrepancy between roentgenographic reports and operative findings. Dandy⁴²⁶ objected to the use of all contrast media for localization and diagnosis of protruded disks, believing this should be accomplished by clinical findings alone with "almost absolute accuracy." [Others disagreed and believe that contrast myelograms are useful in diagnosis when properly employed.—Ed.]

A new method for detecting and localizing protruded disks involved study of roentgenograms made while the patient performed extension, forward flexion and lateral flexion to both sides.^{488, 1023} A somewhat similar plan was described by Gianturco: tracings of spinal roentgenograms made with the patient in the erect and in the forward and backward flexed positions were superimposed. The method was applied especially to lesions in the fourth and fifth lumbar interspaces. Abnormal motions were recognized for which disease of the disk was commonly responsible. No conclusions were reached regarding practical application of these methods.

New maneuvers for physical diagnosis of protruded disks were described. The patient lies supine with knees flexed over the end of the examining table in order to increase the lumbar lordosis. In this position sacral and lumbar roots are relaxed. But the pincer action of hyperextension tends to increase the protrusion of the disk. In a typical case, there is first a latent period followed by steadily increasing peripheral pain. Upward pressure on the painful leg with traction on the painless leg produces pain which also appears after a latent period (Duncan and Hoen).

Narrowed intervertebral spaces do not necessarily indicate the presence of protruded disks. Many instances represent congenital anomalies at the lumbosacral junction. Narrowed disks were found in three (1 per cent) of 300 children between the ages of five and 15 years. None had any evidence of fracture, infection or trauma. The condition probably represented sacralization of the fifth lumbar vertebrae. Six cases were reported in which narrowed lumbosacral interspaces were noted in association with low back pain caused by other lesions (Vinke and White).

Treatment of Protruded Disks. The proper treatment of herniated disks will be debated for years to come (Poppen¹⁴⁰⁴). Conservative management is usually preferable as recovery without operation ensues in a large proportion of cases. Once herniation of a lumbar disk has developed, the patient should always protect his back from undue stooping, lifting and strain. Operation should not be expected to restore a pathologic disk to normal.⁹⁶¹ Surgery should be used

when conservative treatment is unsuccessful, but ultraconservatism should not be practiced. When satisfactory progress is not being made after a few weeks of rest in bed, traction, use of casts, brace or belt or when a clear diagnosis of large complete herniation can be made, surgery is indicated.⁹⁰¹ Continuing intolerable pain or damage to nervous structures also provides justification for operation.

When operation is indicated the complete removal of all the degenerated cartilage was advised. Care should be taken to detect and treat multiple lesions if present. Operations currently in use do not significantly alter the supporting structure of the back and yield good results in most cases.^{201, 499, 1126, 1597, 1951, 1911}

In advance of operation, a decision should be made as to whether spinal fusion is indicated. Although indications for fusion are not precise, most writers believe that fusion should be done when complications are present, such as spondylolisthesis or other anomalies which may cause instability.^{77, 452, 543, 572, 1333, 1404, 1423, 1474, 1597} Dandy^{427, 428, 429} believed that fusions are never indicated but Farrell and McCracker⁵⁴³ considered results of fusion alone as good as those from laminectomy.

Although most writers recommended excision of the offending disk at operation, Ecker⁵⁰³ considered that small or moderate intraspinal protrusions responded to decompression of the nerve root, that is, removal of the articular capsule to which the lateral portion of the ligament is attached. This operation gave him results as favorable as those from removal of the disk.

Intervertebral Foraminotomy. Opening of the intervertebral foramen by removal of facets and their articular processes was recommended by Bankart⁷⁰ in cases in which (1) simple laminectomy failed to reveal protruding disks, (2) the disk space had collapsed completely, (3) "spine surgery with or without fusion" failed to relieve sciatica,²¹² and (4) severe sciatica occurred.

SCIATICA: GENERAL COMMENT

Sciatica is a symptom of many conditions, including: (1) lesions within the nerve itself, or its central connections; (2) irritation or compression of the nerve or its central connections from nearby disease, and (3) pain referred from disease in distant structures. Even hysteria may cause sciatica.⁸⁵³ Many cases are caused by fibrositis according to Jackson.⁹⁰⁴ [Difficult to prove.—Ed.] Sometimes no cause seems apparent even after exhaustive study.^{20, 904} In one case sciatica was caused by an aneurysm of the sciatic artery which pressed on the sciatic nerve in the buttock (LeCocq).

Epidural or perineural injections of saline, metycaine or procaine were again recommended.^{121, 675, 676, 680, 1162, 1782, 1985}

An anatomic study of the relation between the lumbosacral trunk of the sciatic nerve and the sacroiliac joint in cadavers was reported (Hershey⁷³). This nerve trunk traversed the lower third of the sacroiliac joint. Hence lesions such as osteoarthritis (which was present in 25 per cent of the bodies studied) seemed capable of producing direct irritation of the lumbosacral trunk and sciatica.⁵⁷³ [Presumably other forms of sacroiliitis (sacroiliitis of tuberculosis or rheumatoid spondylitis) could similarly cause sciatica.—Ed.]

SPECIFIC INFECTIOUS SPONDYLITIS

For discussion see comments on spondylitis under "Tuberculous Arthritis," "Syphilitic Arthritis," "Brucellosis; Undulant (Malta) Fever" and "Typhoidal Arthritis."

RHEUMATOID (ANKYLOSING) SPONDYLITIS

Historical Data. The original papers by Bechterew, Strumpell, Marie and Leri, and others were reviewed (Dunham and Kautz).

Etiology. Trauma, exposure, focal and other infections, psychic strain, gonorrhea and preceding ill health are not the cause of the disease but are only provocatives; sometimes no provocative factor is found.¹⁷⁶ Brucellosis was considered by Goldfain⁶⁶⁴ the cause of five typical cases of ankylosing spondylitis, indistinguishable from rheumatoid spondylitis except for the "quite positive skin, agglutination and opsonic index tests for brucellosis."

[That brucellosis may cause rheumatoid spondylitis, in contrast to localized *Brucella* spondylitis, remains to be proved. Possibly these five patients had brucellosis unrelated to a coincidental rheumatoid spondylitis. The cause of rheumatoid spondylitis remains unknown.—Ed.]

Incidence. Rheumatoid spondylitis is, contrary to general belief, a fairly common cause of backache in young men. Of 1,000 new "run of the mill civilian patients" two (0.2 per cent)⁸³² had this disease. It was more common among military personnel, and affected 5.2 per cent of 270 rheumatic British soldiers (Savage¹⁵⁴¹), 18 per cent of all soldiers with chronic backache at an American army general hospital.¹⁷⁶ It affected 120 (0.4 per cent) of 27,031 such patients seen by Dekkers.

The condition generally appeared in adults between 20 and 40 years of age.⁶⁰⁸ Although 47 per cent of Fletcher's⁵⁶⁸ 68 patients were females [far out of line with the usual sex incidence—Ed.], males in other series were predominantly affected, comprising 91 per cent of McWhirter's 168 patients, 87 per cent of Goldfain's 18,⁶⁶⁴ all of the 20 patients of Dunham and Kautz⁴⁸⁹ and all of the 100 soldiers seen by Boland and Present.¹⁷⁶

Clinical Data. The usual symptoms, signs and laboratory data were considered.^{59, 148, 176, 244, 489, 568, 608, 811, 832, 1212, 1444} Earliest symptoms were often insidious backache or transient sciatica, sharp pain or catches in buttocks or lower part of back, girdle pains, fatigue, gradual spinal stiffness. Spinal flexion may cause pain that extends into neck, jaw, thorax, substernal or precordial regions (Niehaus).

Small dilated intracutaneous veins of the chest wall are often associated with rheumatoid spondylitis. Such veins were noted by Burrett and Scherf in 70 per cent of patients with cardiac or pulmonary disease, in 69 per cent of those with such miscellaneous conditions as diabetes and peptic ulcer, without notable pulmonary or cardiac disease. Presumably the dilatation of these veins was caused by increased intrathoracic pressure from coughing and sneezing, or the presence of incompetent valves in the affected veins.

Four cases of paravertebral abscesses with *localized* ankylosing arthritis of the apophyseal joints at the level of the soft-tissue abscesses were noted by Oppenheimer.¹³¹⁹ The abscesses, resembling carbuncles of neck or back, were present at the level, not below, the involved vertebrae. Vertebral ligaments were ossified but there was no osseous destruction. Presumably the abscesses were the cause, not the result, of a "localized form of Strumpell-Marie disease or ankylosing (rheumatoid) spondylarthritis."

[It is difficult to believe these were cases of true rheumatoid spondylitis. But it would appear that the abscesses did provoke localized (nonspecific?) pathologic reactions similar to those of the usual disseminated rheumatoid spondylitis.—Ed.]

Laboratory Data. The average concentration of fibrinogen in plasma was slightly but insignificantly higher (559 mg.) in spondylitic patients than in those with peripheral rheumatoid arthritis (520 mg.) (Mester^{122f}). As a diagnostic aid Mester's test (leukopenia from intracutaneous injection of salicylic acid) was grossly unreliable (Green and Freyberg⁶⁰⁶). Calcium and phosphorus metabolism were normal in two cases.¹⁰¹¹

1. *Cerebrospinal Fluid.* The spinal fluid protein was increased (45 to 121 mg. per 100 c.c.) in 29 per cent of 42 patients with rheumatoid spondylitis (with or without peripheral rheumatoid arthritis), in only 7 per cent of 59 rheumatoid patients without spondylitis.¹¹³¹ Abnormalities in colloidal gold-curves were less common: present in 15 per cent of the spondylitics, in 8.5 per cent of the rheumatoids without spondylitis. Concentrations of sugar and chlorides, and manometric pressures were normal. Because the spinal fluid abnormalities occurred four times as often among spondylitics as among those without spondylitis there seemed to Ludwig, Short and Bauer¹¹³¹ to be a relation between the abnormalities and the presence of the arthritic inflammation in spinal and sacroiliac joints. Perhaps they are "due chiefly to an increased permeability of the spinal-cord membranes as a result of their proximity to acutely inflamed articular tissues."

2. *Roentgenograms.* Sacroiliac joints are usually those first affected.^{176, 180, 565, 811, 826, 1408} Earliest changes were blurring of the articular borders, increased density, spotty osteoporosis of juxta-articular bone; later narrowing of joint space; finally ankylosis with "honey-combed" appearance of the lower portion, and cystic caries of margins.

Roentgenologic evidence of involvement of apophyseal joints was considered an essential finding in rheumatoid spondylitis by Oppenheimer,¹¹¹⁸ but not by Boland and Present.¹⁷⁶ Sacroiliac involvement was present in only 60 per cent of Oppenheimer's¹¹¹⁸ cases in which early apophyseal changes were present and in only 86 per cent of his total 50 cases, in all of which characteristic apophyseal lesions were noted. Other lesions noted were rarefaction of vertebral bodies in 52 per cent (neither a constant nor an early sign) and ossification of vertebral ligaments in 50 per cent of all cases. Involvement of costovertebral joints or of pubic symphysis, ossification of muscles or tendons about the pelvis, and rarefaction of pubic bones were noted in certain advanced cases. Even when special techniques for roentgenographic study were used Boland and Present¹⁷⁶ found lesions in apophyseal joints to be less definite and constant than those in sacroiliac joints. In none of their cases were changes in apophyseal joints found without accompanying evidence of sacroiliitis. When apophyseal changes were found, usually only a few scattered apophyseal joints were affected while intervening ones appeared normal.

Pathology. The pathologic changes in a spine studied at necropsy involved the apophyseal joints and the intervertebral symphyses (Freund⁵⁶⁷). Lesions in apophyseal joints were similar to those of rheumatoid arthritis of peripheral joints. In the vertebral symphyses the disks had been partially replaced by vascular connective tissue as a result of invasion from the underlying bone. At the margins of disks, ossification had taken place and true osseous bridges were found. This ossification of disk margins was considered responsible for the bamboo appearance. The intervertebral ligaments, which are generally considered to be the site of the pathologic process producing the bamboo appearance, were spared.

Treatment. 1. *General.* The use of rest, physical therapy, corrective exercises and orthopedic supports was reviewed.^{53, 714, 489, 568, 570, 1075} Concentrated vitamin D was recommended by some,^{1011, 1081} but not used by most writers.

2. *Roentgen Therapy.* Recommended for some years chiefly by Kahlmeter in Sweden, and Scott in England, roentgen therapy has not been used much in this country as yet. Although Smyth, Freyberg and Peck¹⁸⁵² found it of little value in rheumatoid arthritis of peripheral joints, it gave notable relief in cases of rheumatoid spondylitis according to Smyth, Freyberg and Lampe.¹⁸⁵¹

Of 52 spondylitics so treated notable subjective improvement occurred in 72 per cent, notable objective improvement (increased chest expansion and spinal mobility) in 50 per cent, significant reductions in sedimentation rates in 41 per cent. Results were excellent for patients who had early spondylitis with the sacroiliac joints only involved: "In this group 92 per cent showed significant, sustained, subjective and objective improvement, and some were completely relieved of all clinical evidence of disease." To ascertain whether results were from psychotherapy certain patients were subjected to the ritual of roentgen therapy but, unknown to the patients, a lead screen blocked the rays. None of these patients obtained significant improvement "but without exception when they were later treated with roentgen rays significant improvement occurred."

The technic employed 200 kilovolts (175 kilovolts, constant potential equivalent) with 0.5 mm. of copper and 1.0 mm. of aluminum, a $\frac{1}{2}$ value layer of 0.9 mm. of copper, a 50 cm. skin-target distance and an output of 50 r (measured in air) per minute with the site of the field approximately 200 to 300 sq. cm. In their first cases Smyth, Freyberg and Lampe¹⁸⁵¹ treated each field three times with 200 r each time. Treatments were given every other day so that the total dose per field was 600 r. In later cases the doses were reduced to 450 r or to 300 r per field (150 r every other day). Usually three series were given to the same field with a month between each series. If symptoms were not completely relieved, or if symptoms developed in new sites additional treatments were given. The usual toxic reactions of roentgen therapy were observed: leukopenia, nausea and vomiting.

[Recently, to reduce the incidence of roentgen sickness, Freyberg⁶⁰⁹ recommended an alternate scheme using lower voltages, wider and fewer portals and smaller doses of the rays (100 to 150 r for three treatments).—Ed.]

Roentgen therapy has since been recommended by many writers in America and England.^{59, 148, 183, 359, 568, 811, 826, 848, 946, 1212, 1218, 1318, 1444, 1973} Good results were claimed both for the wide field, scattered roentgen-ray technic¹⁴⁸ recommended by Scott, and the concentrated local treatment method of Freyberg.^{848, 946, 1318, 1444} A variety of technical factors were preferred by various writers; for these, reference should be made to the original papers.

When spondylitic women receive roentgen therapy, it should be given carefully with the proper use of filters to prevent sterilization.⁸¹¹

Although most observers noted no significant roentgenographic improvement after roentgen therapy, Oppenheimer¹³¹⁸ noted "a surprising change" in the roentgenologic appearance in four early cases. Joint spaces, previously clouded and apparently filled with bone before treatment, were said to have become radiolucent and clearly defined after treatment. These patients were presumably cured as no recurrences occurred during 18 months of observation. [Not a certain cure.—Ed.] In advanced cases, the roentgenographic lesions were irreparable but roentgen therapy gave "considerable subjective improvement."

How roentgen therapy presumably improves such patients is not known. Blair suggested that benefit might result from "liberation of sulfur within the

body in such a form that it can replenish a sulfur deficiency in any part of the body." [But there is no evidence of sulfur deficiency in this disease.—Ed.]

Most writers urged that roentgen therapy not be relied on solely for treatment. Postural exercises, orthopedic measures, physical therapy, regulated rest and attention to diet should be used to supplement roentgen therapy.

3. *Gold Salts.* Through the years those experienced in chrysotherapy have reported disappointing results in spondylitis. Among recent reports on chrysotherapy few cases of spondylitis were mentioned; in some results were not analyzed separately. Logefeil and Hoffman gave gold in 14 cases of spondylitis of the spine ("atrophic or mixed type"). Results were as follows: "arrested" in two cases; improvement marked in two; moderate in five; slight in four; none in four. [Although treatment was given in "14 cases," results were reported for 17.—Ed.] Others were unimpressed by their results. No significant results were noted by Graham and Fletcher in eight cases, by Winkler¹⁹⁴⁵ in four. Improved was only one of seven patients treated with gold salts by Cecil, Kammerer and De Prume. "This type of arthritis appears to be refractory to gold treatment."

4. *Endocrines.* Because the disease affects females so rarely, certain physicians have been tempted to treat male spondylitis with female hormones. A male spondylitic, given estrogenic substance (weekly injections of theelin; total about 52,000 units in nine injections) developed swollen, painful nipples which necessitated discontinuance of treatment. Subjective improvement but no objective benefit was noted (Solomon¹⁹⁷⁰). Presumably improved were a few patients given stilbestrol "to enhance the effect of vitamin E" (Stone), also two patients given adrenal cortical hormone (Lyon¹¹³⁸).

To "check excessive ossification by inducing decalcification" Mandl implanted into the posterior rectus sheath pieces of thyrotoxic goiter "several times" in each of four patients: two were "markedly improved" but one had a relapse after eight months.

5. *Surgical Procedures.* Preliminary results from vitallium cup arthroplasty of hips was "better than anticipated," but not marked: of 19 cases results were good in only 16 per cent.¹³⁹ Osteotomy of laminae and articular facets was performed by Smith-Petersen, Larson and Aufrane¹⁶⁴⁵ in six cases of spondylitis with marked spinal flexion. Distinct postural improvement resulted when the lumbar spine was operated on, but not when the thoracic region was treated.

OSTEOARTHRITIC (HYPERTROPHIC) SPONDYLITIS

The problem of spinal osteoarthritis is a dual one which concerns lesions of vertebral symphyses (articulations formed by two vertebral bodies and the intervening disk) and of vertebral apophyseal joints. Oppenheimer's¹³²¹ views thereon were restated. To distinguish the two lesions Fletcher⁵⁰⁹ suggested the names "marginal polyspondylitis" for the disease of vertebral symphyses, and "osteoarthritis of apophyseal joints" for the latter condition.

Symptoms of Cervical Osteoarthritis. Common symptoms were pain, rigidity of neck, painful shoulder, headaches, earache, sinus pains and muscular weakness of hand or arm.^{970, 1230} Headaches from irritation of upper cervical roots by osteoarthritis are mainly occipital, generally chronic, recurrent and coming in sieges lasting for days (Chamberlain). In some cases the headaches occurred daily. Neckache referred to shoulders and arms sometimes occurred.

A special type of spinal osteophyte was described by Lyon¹¹³⁹ who used the term "uncovertebral osteophytes" to refer to those affecting the lateral and postero-lateral lips of the superior surfaces of the third to the seventh cervical bodies. These he found some distance laterally and posteriorly from the anterior longitudinal ligament. Uncovertebral osteophytes were attached to the uncinatè processes, the lateral lips of the superior surfaces of the bodies of these particular vertebrae. Oblique roentgenograms were the best means for their demonstration. Most of the affected patients complained of "neuralgic symptoms of arms, neck and back of head." These consisted of boring brachial pain extending down one or both arms, tingling sensations in fingers, pain in shoulders and back of head, dizziness, headache, earache, dysphonia and transitory swelling of hand or forearm. Muscular strength was sometimes impaired, but distinct sensory symptoms were rarely noted. Treatment recommended included rest with a roll under the neck, local heat, cotton bandaging and sometimes "injections of procaine into the affected plexus."

Laboratory Data. Calcium and phosphorus metabolism was normal in two cases (Klassen and Curtis¹⁰¹¹).

Treatment. The use of Sayre's extension apparatus for the treatment of cervical osteoarthritis was again described (McFarland and Krusen).

Radiant heat is first applied for 30 minutes, then massage to neck and shoulders. Traction (70 to 80 pounds [31.8 to 36.3 kg.]) is then applied slowly by means of the sling. The head is gently rotated to right and left after which traction is released slowly. This procedure is carried out twice daily for a week or more; then the patient is instructed to use the sling at home. If relief occurs, it usually begins to appear after three or four treatments.

Study of roentgenograms made during traction showed an average increase of 1.09 cm. when measured along the tips of the spinous processes, 0.65 cm. when measured along the posterior margins of the bodies, and 0.28 cm. along the anterior margins of the bodies. A tendency to straighten the normal cervical curve was noted and the diameters of the intervertebral foramina were increased. Widening of neural foramina seemed to offer a reasonable basis for the use of head traction in osteoarthritis.

"When symptoms presumably due to spinal osteoarthritis increase despite treatment, think of coincidental metastatic carcinoma." An illustrative case was reported (Buttorff²⁷²).

GOUT AND GOUTY ARTHRITIS

The recognition of "gout, the physician's shame,"¹²⁹⁶ is important because acute gouty arthritis is, of all articular diseases, most responsive to treatment. Current writers continued to stress the matter of early diagnosis.^{726, 812, 1666, 1820} Interesting reviews appeared⁷⁸ including one on "milestones in the diagnosis and treatment of gout" (Neuwirth¹²⁹⁶).

Incidence. Gout was diagnosed 79 times within five years at the Cleveland City Hospital (Solomon and Stecher¹⁶⁷⁴). Of 177 cases at the Cleveland Clinic 80 per cent were in the "executive class"; 10 per cent were physicians (Haden⁷²⁶).

Factors Governing Incidence. 1. *Heredity.* The presence of a hereditary factor of some cases of gout was confirmed. Among groups studied, the familial incidence was 10,¹⁶⁷⁴ 11,²¹⁴ 14¹¹⁸⁰ and 18 per cent.⁹⁰² Smyth and Freyberg¹⁶⁴⁹

studied the families of two gouty persons: seven of the eight adult male members of the two families had hyperuricemia, and five had clinical gout. None of the females gave evidence of the disease. Talbott¹⁷⁶⁵ studied 136 blood relatives of 27 gouty persons. Although none "was suffering from gout or gouty arthritis" hyperuricemia (values for serum uric acid of 6.1 to 10.8; average 7.3 mg. per 100 c.c.) was present in 25 per cent. Relatives of gouty persons should be studied for the presence of unsuspected gout. According to Gibson⁶¹⁸ and Bauer⁸⁰ clinical gout frequently skips a generation. [No statistics given.—Ed.]

2. *Sex.* Of recent cases of gout 3 to 10 per cent were in females (3,²¹⁴ 5⁷²⁶ and 10 per cent^{1180, 1674}).

3. *Age.* The age at the first acute articular attack varied between 15 and 71 (average 47.7) years in one series,²¹⁴ between 20 and 73 years in another.¹¹⁸⁰ Fifty-one²¹⁴ and 64 per cent¹¹⁸⁰ of patients were first affected between 40 and 60 years of age.

4. *Race.* Most patients were of American parentage; next often affected were those of Italian parentage.^{726, 1180} Two Negro brothers had the disease.³³⁰

5. *Dietary Habits.* Of one group 40 per cent were "obese"¹¹⁸⁰; of Haden's⁷²⁶ patients 30 per cent were 40 pounds (18.1 kg.) or more overweight; of Brøchner-Mortensen's²¹⁴ 100 patients the majority were overweight and 50 per cent drank at least five bottles of beer daily. But among aged beer-drinking pensioners Howell noted a low incidence of gout, and in India gout occurs in teetotalers and vegetarians (Sahai). Most of the 79 gouty patients of Solomon and Stecher were either on relief or their incomes were too low for them to purchase much meat. [No estimate of the diets was given.—Ed.]

[Intake of liquor and purines probably has no influence whatever on the incidence of the disease, gout, but some workers believe that such intake may be notably related to the incidence of attacks of acute gouty arthritis. Unfortunately writers failed to make this distinction or to analyze their cases from this standpoint.—Ed.]

Clinical Data. 1. *General.* Data on 413 new cases were reported: on 38 by Bärtels, on 46 by Steinberg¹⁷⁰⁷; on 50 by McCracken,¹¹⁸⁰ on 79 by Solomon and Stecher and on 100 cases each by Haden⁷²⁶ and by Brøchner-Mortensen. An excellent textbook chapter on gout was written by Bauer and Klemperer.⁹² The clinical and diagnostic features and complications of gout and gouty arthritis were reviewed by Hench.⁸¹²

A larval stage of gout, relatively symptomless, is present for some time before acute arthritis appears; it may be characterized by hyperuricemia, renal colic, rarely tophi (Hench⁸¹²). In two of Talbott's cases¹⁷⁶⁴ renal colic developed from urate stones months or years before the first attack in joints.

Haden⁷²⁶ considered gout "a disease of well people," but Bartel's patients would hardly agree: 14 whose disease had lasted an average of 11 years had lost an average of 20 months of work and an average salary of \$3.640 with additional medical expense averaging about \$500.

The big toe was first affected in 53,^{726, 726} 70,²¹⁴ and 60 per cent⁸¹² of cases. It was involved at some time in 95 per cent.¹⁶⁷⁴ An ankle was first affected in 13, the foot in 12 per cent of Haden's cases.⁷²⁶ Hips were affected at some time in 2 per cent of Lockie's cases. Myositis is a common feature of gout, according to Hopkins.⁸⁶²

[We do not agree. No statistics or clinical evidence were presented in this vague paper. Gouty tendinitis occurs but acute or chronic myositis, certainly gouty and responsive to

colchicine, is rarely if ever seen in gout. Among the 400 cases of gout currently analyzed no instance of gouty myositis was found.—Ed.]

Of 100 gouty patients nine had had rheumatic fever, six of whom died of cardiac insufficiency (Brøchner-Mortensen).

2. *Provocatives.* Trauma, dietary indiscretions, infection and certain medications were common provocatives (Brøchner-Mortensen²¹⁴; Hench⁸¹²). For diagnostic purposes McEwen¹¹⁹⁷ used high fat or high purine diets: each of five gouty persons fed a high fat diet (two weeks may be necessary) had acute attacks. High purine diets produced much greater hyperuricemia but were not more successful than high fat diets in inducing gouty attacks. But Bauer⁸⁹ could not relate acute attacks to dietary indiscretions. Changes in barometric pressure may be related to acute attacks: many prodromata accompany a fall in pressure (Talbot¹⁷⁶⁴).

Surgical operations are prone to provoke gouty arthritis: "In cases of acute post-operative arthritis suspect gout" (Hench⁸¹²). The value of this axiom was confirmed. Of Linton and Talbot's gouty patients subjected to 22 surgical operations post-operative arthritis developed in 86 per cent. In five cases of gout reported by Ficarra and Adams acute arthritis developed within three to five days after operation.

3. *Tophi.* In recent series subcutaneous tophi were present in 21,^{725, 726} 28,¹¹⁸⁰ 33,²¹⁴ and 48 per cent.^{89, 812} Tophi were absent in three females²¹⁴ and in 17 males whose disease had been present 10 to 30 years.^{725, 726} Osseous tophi (roentgenographic areas of erosions) were present in 25,^{725, 726} 27¹⁶⁷⁴ and 31²¹⁴ per cent.

4. *Complications.* Urate stones or gravel are passed by about 11 to 23 (average 13) per cent of patients at some stage of their gout, and "gouty nephritis" affects an average of 22 per cent (Hench⁸¹²). Renal stones were passed by 11 per cent of Haden's patients,^{725, 726} by "several" of Talbot's patients,¹⁷⁶⁴ by 15 per cent of Brøchner-Mortensen's 100 patients²¹⁴ but by only one of Steinberg's¹⁷⁰⁷ 46 patients. Chronic glomerulonephritis and nephrosclerosis each occurred in 7 per cent of Brøchner-Mortensen's 100 cases.²¹⁴ Systolic blood pressure was more than 150 mm. of mercury in 48 per cent of one series.²¹⁴ But only 30 per cent of Steinberg's patients¹⁷⁰⁷ had hypertension: "Gout is not an etiological factor in hypertension" nor did Steinberg¹⁷⁰⁷ believe that gout predisposes to renal irritation or angina pectoris. Gouty persons are likely to have glycosuria or "potential diabetes" according to some,⁶⁴⁸ but not according to others.²¹⁴

5. *Unusual Clinical Data.* Of 168 patients with polycythemia vera 4.8 per cent (eight) had gouty arthritis, an incidence higher than mere coincidence would allow (Tinney, Polley, Hall and Giffin); a previously reported case of gout with polycythemia and subleukemic myelosis ended fatally (Reifenstein¹⁴⁴⁷). A case of severe gout with macrocytic anemia was noted (Sahai), also a fatal case of severe tophaceous gout with marked microcytic anemia (Lambie and Davis) and a case of severe gout with nontropical sprue (Morlock and Rosenberg). Pederson studied a case of extensive calcinosis in a male with acute recurrent gouty arthritis and hypogonadism¹³⁵⁶: apparently calcinosis made its appearance at age 10 years, gouty arthritis at age 30 years. Urates were not found in the calcific deposits.

[No mention of therapy by vitamins was made in this case. Recently a few cases of gout have been seen with extensive calcium deposits in urate tophi and elsewhere resulting from improper use of concentrated vitamin D on the assumption the patients had rheumatoid arthritis.—Ed.]

Diagnosis. Criteria for diagnosis were outlined in 21 axioms by Hench.⁸¹² Provocative tests with diets were valuable only if positive; McEwen¹¹⁹⁷ found the high purine provocative diet was more agreeable but no more successful than a high fat diet. But Talbot¹⁷⁶⁴ considered it unnecessary to precipitate an attack

to justify a diagnosis. Of one group the diagnosis was made in the first attack in only one out of five cases (20 per cent) (McCracken ¹¹⁸⁹). When any male suddenly develops acute monarthritis, gout should be considered even though a joint other than a big toe is affected.^{725, 812}

Pathology. 1. Joints. One patient at necropsy presented extensive urate deposits in many joints, but no subcutaneous tophi were present.¹¹⁶⁵ Urate deposits are rarely found in sacroiliac joints, joints of spine or jaw (Bauer ⁸⁹).

2. Kidneys. At necropsy kidneys of three gouty patients were studied^{37, 1058, 1165}; in two of the three the kidneys contained urate deposits.

3. Other Tissues. Although urates in large tophi often surround blood vessels or nerves, they do not affect or invade them (Linton and Talbott ¹¹⁰⁸). In four of eight cases "cirrhotic changes" affected livers at necropsy²¹⁴; pathologic changes also affected kidneys in seven, heart in seven and aorta in eight cases. In the case of Lambie and Davis ¹⁰⁵⁸ lesions of bone marrow, kidney and heart were of special interest. [Were the specimens preserved in a formalin-containing fixative, rather than absolute alcohol? If so, the local cardiac intraventricular lesion may have represented a rare intracardiac tophus spoiled in preparation.—Ed.]

Laboratory Data. 1. Blood Uric Acid. Talbott ¹⁷⁶⁴ again insisted that practically every gouty patient presents hyperuricemia, but others disagreed. Fifteen to 20 per cent of gouty patients were found by others to have normal uric acid concentrations in blood or serum. Thus the serum uric acid was increased in 80 per cent of 95 patients²¹⁴; blood urates were increased in 86 per cent of Haden's cases⁷²⁵; blood levels of uric acid were below 5 mg. per 100 c.c. in 18 per cent of McCracken's 50 cases.¹¹⁸⁹ According to Hench ⁸¹² 75 per cent will have hyperuricemia at some stage of gout.

Patients often take large doses of aspirin shortly before blood uric acid studies are done; this markedly decreases the concentration in the blood. Patients should avoid urate eliminants for 48 hours before blood tests (Lockie; Talbott ¹⁷⁶⁴). Gouty patients without renal insufficiency clear urates normally and may excrete large amounts of urates (Talbott ¹⁷⁶⁴).

To determine uric acid the method of Folin or Benedict was recommended. Neither test offers undue technical difficulties but only great care in preparing reagents and frequently checking controls assures reliable results (Bauer ⁸⁹).

2. Sedimentation Rates of Erythrocytes. Rates were increased, often markedly, during attacks, but returned to normal generally soon, sometimes tardily thereafter.^{214, 725, 726, 728, 1115, 1189}

3. Miscellaneous Tests. Data on liver function tests, blood counts and other laboratory tests were reported by Bröchner-Mortensen.²¹⁴ Various tests for abnormal colloidal states in blood were applied by Milles and Salt ¹²⁴⁴: formol-gel test, Weltmann reaction, Takata-Ara reaction. No changes were specific for, or characteristic of, gout.

Etiology. Opinions on etiology were summarized.⁸¹² Gout was considered a manifestation of deranged purine metabolism,¹⁶⁷⁴ a condition related to increased formation of uric acid¹⁷⁶⁴ or to abnormal deposition of urates.⁶⁴⁹ Lead poisoning was not a factor in 100 cases.²¹⁴

[No new data of significance were presented. The cause remains unknown.—Ed.]

The causes of acute gouty arthritis may be quite different from the cause of gout. Postoperative gouty arthritis was considered by Tuohy to result possibly

from postoperative ketosis incident to a low dietary intake.¹⁸²⁰ But in five such cases Ficarra and Adams⁵⁵⁵ noted hypoproteinemia (4.5 to 5 mg. per 100 c.c. of plasma). The hypoproteinemia (from a low postoperative intake of protein) was thought to stimulate endogenous purine metabolism, resulting in "hyperuricemia which is the precipitating agent for the formation of tophi or an osteoarthritic gout."

[It has not been proved that acute attacks result from, or are associated with, urate deposition in joints, nor that hyperuricemia bears any consistent or causal relation to acute attacks.—Ed.]

Treatment. Usual principles were restated.^{89, 812, 1764} No new successful remedies were described. Gout itself is incurable; patients will have the disease through life.¹⁷⁶⁵ But much can be done to control the frequency and severity of acute attacks.^{79, 812, 1686} Hereditary candidates and hyperuricemic relatives of patients with active gout should live moderately and avoid obesity and the various provocatives of acute gouty arthritis.^{812, 1765}

1. *Treatment of Attacks.* Colchicine should be given until pain is relieved or gastrointestinal symptoms occur.^{93, 812} Patients who recognize prodromata of an attack may abort attacks by prompt use of colchicine. "It is better to take a few tablets of colchicine for a false alarm than to permit an attack to become established" (Hench⁸¹²). Calomel and a saline aperient were prescribed by Ball. Absolute rest in bed is usually indicated; premature resumption of normal activity may precipitate a flare-up. The use of physical therapy after attacks "to absorb exudation and prevent residual fibrosis" was recommended by Solomon and Stecher. [Physical therapy, except for the use of hot or cold compresses, is generally unnecessary. More strenuous measures (baths, massage) may provoke an exacerbation, a "cure-crisis."—Ed.]

2. *Interval Treatment.* Most writers favored the use of interval therapy. Some who have formerly discounted its value now at least recommend the prophylactic use of colchicine. The usual interval treatment included diets low in purine and fat, high in carbohydrates and the periodic use of salicylates or cinchophen.^{79, 303, 812, 1296} Restriction of purines presumably relieves the already overburdened metabolizing mechanism, and may at least lessen the amounts of urates available for ectopic deposition. A low fat intake prevents retention of purine, a high carbohydrate intake favors elimination of endogenous urates. A variety of detailed menus offers welcome aid to the gouty.⁶³⁶ Some physicians prohibited the use of alcohol^{79, 812}; others suggested that it be regulated by rules of temperance rather than abstinence.¹⁷⁶⁵

Although many now prefer salicylates as a urate diuretic,⁸¹² Bartels administered cinchophen three days a week; as treatment progressed he made periodic estimations of the concentration of serum uric acid; when it was reduced cinchophen was given only twice or once a week and when it approached normal, cinchophen was not given. According to Bauer⁹³ large doses of salicylates need not be given continuously except to patients with rapidly recurring gouty arthritis. The site of action of cinchophen and salicylates is probably the renal tubules: the drugs inhibit resorption of urates. To increase the solubility of urates alkaline powders were used.^{812, 1765}

A patient given 17 c.c. of pure sterile uricase within four days experienced no untoward local or general reaction but also no reduction of articular pain or swelling and no lowering of plasma uric acid (Oppenheimer and Kunkel). The dosage was probably "far too small."

Colchicine as a prophylactic has through the years been considered useless. But some are now reviving its use. Talbott's plan¹⁷⁶⁵ follows: for patients who have only one attack each year, "a few colchicine tablets" (each gr. 1/120 [0.00053 gm.]) only

when mild articular aches and pains appear. [Patients do not refer to such minor episodes as "attacks" and do not include them when asked about attacks.—Ed.] Talbott recommended for others who have only one attack a year one or more tablets a day to one or two a week; for those with more than two attacks yearly, two or three tablets daily for two to three days a week; for patients with severe gout, one to three tablets daily continuously. Several patients followed this last schedule for as long as five years with no intolerance or untoward effect. [One of us, L.M.L., recently saw a patient who had taken colchicine, 1/120 grain (0.00053 gm.) three times a day for five years with no reaction. It had been prescribed by a psychiatrist; the patient thought it was a sedative.—Ed.] Tolerance to the drug did not occur and if an acute attack occurred full doses of colchicine were effective. According to Talbott¹⁷⁶⁵ such intermittent use of colchicine may abort mild attacks, convert severe attacks into mild ones, keep the patient "colchicine-conscious" and alerted to use it promptly when an attack occurs.

[From this it would appear that colchicine in his hands has not prevented all attacks. Nevertheless continued studies are in order.—Ed.]

Three regimens to prevent postoperative gouty arthritis were reported. Hench⁸¹² used a purine-free diet and salicylates or cinchophen five days before and five days after operation. Linton and Talbott^{1108, 1765} recommended the use of colchicine, three tablets daily (each 1/120 grain) for two or three days before and after operation. Thus the incidence of postoperative arthritis was reduced from 86 to 8¹⁷⁶⁵ or 10 per cent.¹¹⁰⁸ Ficarra and Adams⁵⁵⁵ recommended the prevention or correction of postoperative hypoproteinemia. [No details given.—Ed.]

3. *Tophectomy*. Large tophi should be removed to prevent or correct ulceration.^{812, 1108} When débridement is done thoroughly, prompt healing occurs. The surgical treatment in 11 such cases was described by Linton and Talbott¹¹⁰⁸ with fine colored illustrations.

4. *Results of Treatment*. An "interval régime" provided to Bartels' patients "indisputable benefit." On this plan only seven minor attacks of acute gouty arthritis occurred in 31 patients as compared with 84 major attacks during a comparable period before treatment. Even patients with chronic gouty arthritis were benefited. Despite instructions, patients often fail to control their gout, not so much because of the limitations of treatment as for other reasons listed by Hench.⁸¹²

Mortality from Gout. Between 1930 and 1939 deaths attributed to gout numbered 2,400 in England and Wales, only 25 in the United States. Possible reasons for this "remarkable contrast" were discussed (Bowerman).

STUDIES ON COLCHICINE

Three patients with severe inoperable carcinoma were given rather large doses of colchicine (13 mg. in four days, 29 mg. in seven days, 28 mg. in 64 days; 0.5 mg. = 1/120 grain). Colchicine poisoning with granulocytopenia developed in the first two. The effect of the colchicine on normal and cancerous tissues was studied at necropsy by Brown and Seed who considered colchicine a dangerous drug capable of producing severe depression of bone marrow. In one case peripheral neuritis of the popliteal nerve was probably caused by the colchicine. The drug exerts a toxic effect on living cells which commonly arrests mitosis at an early stage, usually the metaphase; it may lead to cell death. The

effect of colchicine is general; it is selective only in the sense that the drug first affects tissues which have the highest metabolism and rates of cell division: bone marrow, skin, lymphoid structures, tumors. Colchicine produces no specific morphologic changes. Other histopharmacologic studies on colchicine were made (McPhail and Wilbur^{1210, 1211}).

[The doses used in the first two cases were perhaps larger than those generally used in acute gouty arthritis. But those who prescribe more or less continuous doses of colchicine for prophylactic purposes should be on the lookout for toxicity: granulocytopenia or neuritis.—Ed.]

CINCHOPHEN TOXICITY

The Council on Pharmacy and Chemistry³⁹⁴ published a report on "The Present Status of Cinchophen and Neocinchophen" with a review of toxic reactions, contraindications and indications. Between 1925 and 1936 were reported about 191 cases of toxic hepatitis with about 88 deaths attributed to cinchophen products: a yearly average of about 16 cases of toxic hepatitis including about seven deaths. The probable fatality rate was one death in 10,000,000 \pm doses. A questionnaire^{393, 394} sent to 266 professors of medicine, pharmacology and pathology revealed that only 14 per cent considered these drugs indispensable; a minority (24 per cent) stated that they had therapeutic effects not accomplished more safely otherwise; only 13 per cent gave them with confidence of safety and only 11 per cent considered that cinchophen toxicity could be satisfactorily counteracted. But 24 replies considered these drugs "particularly useful in the treatment of gout." The Council concluded: "The drug should not be employed unless the attending physician feels that the patient's need for it fully justifies the risk, possibly for the relief of pain in certain cases of so-called rheumatism, including gout, and some types of arthritis when safer substitutes fail to afford relief." But others concluded the fear of cinchophen has been exaggerated.^{496, 726, 812, 1435, 1436, 1437} A review of toxic reactions, and experiences with gout suggests that certain patients, especially rheumatoids, may be somewhat more susceptible to cinchophen toxicity and that gouty patients may be relatively safe. Certainly the majority of cases of toxicity have been in cases of rheumatoid arthritis and very few indeed in the gouty.

Two deaths presumably related to cinchophen were reported. A woman, aged 56 years, presumably with rheumatoid arthritis of six weeks' duration was twice given typhoid vaccine intravenously (Yott) (first dose 10,000,000, second dose, 25,000,000 bacilli). Three days after the second reaction icterus appeared, later coma and death in three weeks from acute yellow atrophy. Unknown to the physician the patient had taken on a pharmacist's advice "small doses of cinchophen" for six weeks.

A woman, aged 38 years, who had had jaundice of unknown type six years before, developed rheumatoid arthritis for which she took oxyiodide (containing cinchophen), duration and amount unknown (Mass¹¹⁶⁴). During the next five years she had recurring jaundice from which she recovered. She died of a perforated gastric ulcer. At necropsy toxic hepatic cirrhosis, presumably related at least in part to the cinchophen, was found.

[In both these cases the rheumatoid arthritis subsided during jaundice.—Ed.]

Among 100 arthritics given cinchophen daily for more than a year no liver damage was found.⁴⁰⁶ Among Rawl's ^{1435, 1436, 1437} 500 patients who had taken cinchophen "over a period of years" no granulocytopenia occurred, but a variety of nonfatal reactions were noted including jaundice in two cases. The use of natural vitamin K seemed to lessen the toxic effects of cinchophen but agranulocytosis developed in one patient given cinchophen and *synthetic* vitamin K. Synthetic vitamin K contains the quinone radical which may produce agranulocytosis.

The production and prevention in animals of gastric ulcers from cinchophen, and the effect of cinchophen on certain liver functions were studied.^{31, 32, 132, 1632, 1633}

[In our previous eight Reviews (1932-1940) ¹ we reported 16 cases of cinchophen poisoning: nonfatal agranulocytosis in two cases, hepatitis in 14 (fatal in nine, nonfatal in five). The drug had been taken as follows: for rheumatoid arthritis in two cases; "chronic polyarthritis" in one; "rheumatic fever" in two; sacroiliac pain in one; pains in chest and shoulder in one; gonorrheal arthritis in one; "rheumatism" in one; osteoarthritis in one; cholecystitis in one; "colds" in two; for unstated reasons in three. No definite case of gout was included unless Kersley's (1937) case ¹⁰ of transitory nonfatal jaundice from one dose given for an unstated disease was in a patient with gout. We must conclude, therefore, that in cases of gout cinchophen toxicity has rarely been reported. Even so we recommend a trial of salicylates before resorting to cinchophen. Only in cases of gout not otherwise controlled, does the use of cinchophen seem justified. In particular we avoid its use in rheumatoid arthritis.—Ed.]

URIC ACID PROBLEM

Methods. 1. *Blood.* The uric acid partition in gout and in hepatic disease was studied by Adlersberg, Grishman and Sobotka. The uric acid partition (the relation of free to bound, nonultrafiltrable uric acid) of normal blood serum is comparatively constant, the bound uric acid comprising 4 to 24 (average 16) per cent of the total serum uric acid. In many diseases this ratio remains normal but in gout and in hepatic disease the free uric acid diminishes, the bound (and the total) uric acid content increases. Gout may be accompanied by signs of hepatic damage; to what extent hepatic dysfunction is related to gout is not known. In 10 gouty patients the bound uric acid content of serum varied from 1 to 65 per cent of the total uric acid content. Gout with marked hyperuricemia may be associated with a normal uric acid partition; but gouty patients with a normal total uric acid content may demonstrate a high bound uric acid ratio. Such findings may have diagnostic and therapeutic significance.

[This interesting work should be studied further.—Ed.]

Other new methods were discussed.^{223, 251} The direct method of Benedict was most suitable for determining uric acid with a photoelectric colorimeter.¹²⁶⁹ Using a new method for preparing phosphotungstic acid, uric acid clearances of human blood were found to average about 15 c.c. per minute, about half that previously reported.¹⁷⁹

2. *Urine.* Discrepancies in various methods for determining urinary uric acid were discussed.¹¹⁰⁰ Based on the action of uricase a method to measure urinary uric acid in the presence of methylated uric acid was developed. This "uricase method" showed that caffeine or theophylline do not increase excretion of "true uric acid" (Buchanan, Block and Christman ^{234, 235}).

Physiology. 1. *Human Beings.* The uric acid content of blood is normal during normal pregnancy, may be increased in toxemias of pregnancy especially just before eclamptic convulsions presumably due to a reduction in glomerular filtration.^{407, 566, 1446}

In pernicious anemia the uric acid content of blood increases when the normoblasts in bone marrow diminish and when reticulocytes in blood increase.¹⁰⁹²

The excretion of uric acid was notably increased by intravenous injections of diodrast but not by hypertonic solutions of glucose, 50 c.c. of 50 per cent glucose (Bonsnes, Dill and Dana). In man there is only a general parallelism, not a specific relationship, between the clearance of uric acid and urea: "it is improbable that the rise in incidence in gout which occurs with aging is primarily due to a progressive and selective impairment of the renal ability to secrete uric acid associated with renal and vascular senescence" (Stieglitz). The metabolism of lactic acid (and the blood levels of lactate and pyruvate) seems to influence uric acid excretion (Michael).

2. *Animal*. Injections of uricase into hens lowered the blood uric acid; the effect of a single injection lasted eight to 24 hours (Oppenheimer and Kunkel^{1325, 1326}). Renin, injected into dogs, increased the uric acid content of blood and urine.¹⁵⁴⁷ Alloxan and dialuric acid, a reduction product of alloxan, injected into pigeons (a single dose of 60 to 125 mg. per kilogram of body weight, less than half the diabeto-genic dose) sometimes caused marked increases in blood uric acid and deposits of sodium urates in all serous membranes (pericardium, pleura, surface and parenchyma of liver, kidneys).⁶⁷⁰

CASE REPORTS

WEBER-CHRISTIAN'S DISEASE: REPORT OF A CASE*

By IVAN L. BUNNELL, M.D., and DEXTER S. LEVY, M.D., *Buffalo, New York*

WEBER-CHRISTIAN'S disease, or relapsing febrile nodular, non-suppurative panniculitis, is a disease of unknown cause, characterized by the appearance of crops of inflammatory and necrotic subcutaneous nodules chiefly on the arms, legs, and trunk and by a definite constitutional reaction. The disease commonly affects young women and generally results in recovery, but runs a protracted course, which may last from one month to 15 years. There are no characteristic laboratory findings. The nodules may regress with fibrosis and atrophy at the original site. A recent review of the literature¹ reveals 28 recorded cases of Weber-Christian's disease, and more recently, a few additional cases have been described.^{2,3} Another case of this disease, proved by biopsy, and possessing several noteworthy features, is reported here.

CASE REPORT

H. B., a 33 year old, single, white woman, was admitted to the Edward J. Meyer Memorial Hospital, October 30, 1944, complaining of nodules of the skin, weakness, chills and fever. During her hospital stay there appeared new crops of subcutaneous nodules accompanied by exacerbation of symptoms. Treatment was supportive only, and the patient was discharged December 29, 1944, free of symptoms and subcutaneous nodules.

History: On entry to the Edward J. Meyer Memorial Hospital the patient stated that subcutaneous nodules had appeared on the arms in August 1944. Later, nodules were noticed on the legs, buttocks and breast. The nodules began as discrete lesions which increased in size and became tender. They occurred in crops, each new outbreak being accompanied by malaise, chills and fever.

In 1942, the patient had a cholecystotomy for "cholelithiasis," following which an incisional hernia developed. From January 1943, to October 1944, there followed five admissions to another hospital for complaints of abdominal cramps, nausea and emesis, loss of weight, chills and fever. The patient's leukocyte count ranged from 15,000 to 26,000 cells per cu. mm. with 84 per cent polymorphonuclear leukocytes. The abdominal symptoms were explained on "subacute intestinal obstruction" for which surgical repair of the incisional hernia was attempted. The diagnosis of the cause of the constitutional symptoms, however, remained obscure; septicemia and generalized vascular disease were considered among the possibilities. Treatment during the five admissions included the administration of sulfathiazole, sulfadiazine, sulfamerazine and penicillin.

History was also obtained that the patient had suffered one "grand mal" convulsion and two "petit mal" seizures in May 1944, following which dilantin was prescribed. There was a family history of bronchial asthma. The patient complained

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From the Department of Medicine, Edward J. Meyer Memorial Hospital, and University of Buffalo, School of Medicine, Buffalo, New York.

of loss of weight of 67 pounds in the past two years, which she attributed to an inadequate diet.

Physical Examination: The patient was a pale, obese, white woman of sandy complexion, moderately ill. Temperature, 99.4; pulse, 118; respirations, 20; and blood pressure, 140 mm. Hg systolic and 100 mm. diastolic. Many fine râles were heard in the base of the left lung. The heart was not enlarged. There was a soft systolic murmur over the precordium. The abdomen showed a grapefruit sized reducible incisional hernia in the right upper quadrant.

In the subcutaneous tissue of the arms, legs, buttocks, abdomen, right breast, posterior chest and fingers were scattered discrete tender nodules ranging in size from 1.0 to 2.5 cm. in diameter, some of which were in short chains. The largest were found in the legs, and occasionally were fluctuant. The skin overlying the nodules was warm and red.

Laboratory Data: The urine was negative. Hemoglobin: 10 grams. Red blood cell count 3,620,000. White blood cell count 17,500 with 10 per cent bands, 61 per cent filaments, 25 per cent lymphocytes, 3 per cent basophiles, 1 per cent eosinophiles. Thirteen blood cultures were negative. The Wassermann test and agglutination reactions for undulant fever were negative. Chemical examination of the blood disclosed: Glucose 90 mg. per cent; cholesterol 86 mg. per cent; calcium 9.8 mg. per cent; and total proteins 7.2 gm. per 100 c.c. The tuberculin test was 2 plus after 48 hours.

The electrocardiogram showed sinus tachycardia with no axis deviation.

On roentgen-ray examination, the heart was full sized. The left lung showed some congestion at the base, which cleared on subsequent films. The skull and long bones were normal.

Biopsy: Biopsies were made of early lesions as they developed and from a late lesion which had been present before the patient's entry to the hospital. In an early lesion the deep parts of the subcutaneous fat tissue showed edema and hyperemia in the septa. Leukocytosis of the capillaries and hemorrhage were present. There was perivascular infiltration of neutrophils and round cells; the latter type of cell predominated. Vascular lumens were patent. The corium revealed only minimal perivascular infiltration. In a moderately advanced lesion, regressive changes were noted in fat cells. There were focal areas of brown pigmentation. The oldest lesion represented a distinct, active, chronic inflammatory and regressive process of non-specific character. The septa were edematous and infiltrated with neutrophils, round cells and eosinophils. Large macrophages, some with foamy cytoplasm, and multinucleated giant cells were seen particularly in the neighborhood of a large fat or oil cyst with granulation in the wall and with necrotic material in its center. Small cysts, sometimes with crystalline material as content, had also formed. In relation to the large cyst lay a focal calcified particle. The endothelial cells of vessels were swollen. There was inflammation in the walls of vessels and perivascular tissue. Regressive changes involved vascular walls. Biopsy of the gastrocnemius muscle disclosed no inflammatory or regressive changes in vessels. Smears and cultures from cloudy, yellow fluid of the large cyst proved negative for bacteria.

Course: During the first 13 days of the patient's hospitalization, the temperature rose to 102.4°, the pulse rate to 120 per minute, and crops of nodules appeared. One nodule developed on the dorsum of the left hand at the site of venipuncture. The temperature and pulse rate leveled off gradually as new nodules appeared less frequently. Biopsy sites showed poor healing. The patient was discharged on the fifty-ninth hospital day with no symptoms and a normal temperature. Treatment had been symptomatic. Three whole blood transfusions had been given on empirical grounds.

Four months after discharge, no nodules were present, and no atrophy was noted

at site of previous nodules on the hand, arms, and legs. The patient complained only of recurrent convulsions, which occurred at intervals of three or four weeks, and for which she had just resumed dilantin therapy.

In June 1945, six months after discharge, the patient suffered a relapse of her disease, necessitating 16 weeks of hospitalization at another institution. This relapse occurred though the only treatment, in the interim, had consisted of dilantin in effective therapeutic doses. Manifestations were identical with those of the first attack, with the difference that the constitutional reaction was more severe, remission longer delayed, and the distribution of nodules more extensive. Many nodules appeared in the breasts and several on the hands. On two separate occasions during this relapse, a site of previous biopsy broke down and drained spontaneously for a day or two. Treatment, again, was symptomatic.

Seen again, one year after discharge from the Edward J. Meyer Memorial Hospital, the patient offered no complaints, being free now of even gastrointestinal symptoms. A successful herniorrhaphy had been performed during the second hospital admission. The surgery had been tolerated well, with the exception that a small crop of nodules appeared in the immediate postoperative period, only to disappear rapidly.

Examination failed to reveal atrophy of the subcutaneous tissue where nodules had been noted previously.

DISCUSSION

From the clinical and biopsy findings, this case fulfills the fundamental requisites of Weber-Christian's disease. The patient was a 33 year old woman whose outstanding complaints were numerous tender, subcutaneous nodules which appeared in crops, and which were accompanied by malaise, fever, and increased pulse rate. It was felt that these symptoms had existed for two years. Other symptoms including convulsions (history), nausea and emesis, and abdominal cramps were best explained on the basis of epilepsy, incisional hernia, and hypertensive vascular disease. Biopsy of clinically typical nodules showed them to be of an inflammatory-regressive character.

Noteworthy features of this case include: (a) atypical distribution of lesions, (b) marked leukocytosis, (c) unusual biopsy findings. A nodule was present in the right breast, where involvement has been rarely encountered. Although a recent review of the literature states in regard to the reported distribution of lesions that only the hands have been spared, clinically typical nodules were observed on the dorsum and finger of the hand of our patient. In evaluating this observation we must admit that the nodule on the dorsum developed following venipuncture.

Our patient ran a persistent polymorphonuclear leukocytosis; only four out of 28 cases compiled by Larkin showed an increase in the white count.

By multiple biopsies of nodules it was possible to study the subcutaneous lesion from early to late phases, and its relation to the overlying skin. Focal calcification was noted in an advanced lesion; this has rarely been seen. An advanced lesion also showed pseudocysts containing fluid, which was proved to be sterile pseudo-pus. While it is felt that liquefaction in nodules represents an unusual manifestation in Weber-Christian's disease, Shaefer⁴ interpreted the break-down, rupture and discharge of lesions of sufficient differential significance to place his case under the label of "liquefying nodular panniculitis." Perhaps it was this factor which led to the poor healing noted in our case at the biopsy

site; and because of the poor healing, elective repair of an incisional hernia was deferred until the second hospital admission.

The cause of Weber-Christian's disease is unknown. Many cases give a history of iodide or bromide ingestion and etiologic significance has been attached to such a history. Our patient was never administered iodides or bromides; however, there was the history of prolonged treatment with many different sulfonamide preparations; the question is raised as to the possible etiologic significance of such therapy.

SUMMARY

A case of Weber-Christian's disease in a 33 year old white woman is reported. Noteworthy features of this case were the presence of nodules on the hand and in the breast, a leukocytosis of 17,500, and focal calcification in biopsies of subcutaneous nodules. There was a history of ingestion of many different sulfonamide preparations. The question is raised as to the possible relation between prolonged administration of sulfonamides and the occurrence of Weber-Christian's disease.

We are indebted to Dr. Samuel Sanes for the description of the biopsy findings.

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PULMONARY EMBOLISM *

By SIMON S. LEOPOLD, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

It has long been recognized that thrombi originating in the right side of the heart constitute a frequent threat of pulmonary embolism.

Many generations of medical students have been taught that sudden tragic deaths from massive pulmonary embolism following laparotomy, or occurring post-partum, resulted from thrombosis of the pelvic veins. An appreciable mortality which varied little in major clinics was thought to be inevitable and unavoidable.

In the past three years, it has been demonstrated beyond reasonable doubt that thrombosis of the deep veins of the legs is the usual cause of postoperative pulmonary embolism.

Thrombophlebitis complicating certain acute infections, particularly typhoid fever and pneumonia, is thought to be a less frequent cause.

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From the Medical Division of the Hospital of the University of Pennsylvania.

There still remains another group of cases in which thrombi develop in the systemic veins, in the absence of all known etiologic causes for their formation. When pulmonary embolism develops under these circumstances, it is extremely likely to remain unrecognized, especially if its symptoms and signs are attributed to some other acute pulmonary disease.

Emboli which reach the lungs originate principally as thrombi which are formed either in the right side of the heart or in the systemic veins. Thrombi of cardiac origin may develop in the auricular appendage and be swept from there into the pulmonary artery and into the lungs. Pulmonary embolism may also result from dislodgement of a thrombus formed in the right ventricle at the site of myocardial infarction. Occasionally, acute or subacute bacterial endocarditis may be present on the right side of the heart, and the development of multiple thrombi on either the tricuspid or pulmonary valve, or both, may produce showers of pulmonary emboli.

Five years ago, a patient with subacute bacterial endocarditis with overwhelming invasion of the blood stream by *Streptococcus viridans*, was seen by the author. Almost all of the valvular vegetations were confined to the tricuspid



FIG. 1. M. M., female, age 50 years. Subacute bacterial endocarditis, with *Streptococcus viridans* septicemia. Note vegetations on tricuspid valve.

valve, and the rapidly fatal clinical course of this disease was characterized by repeated episodes of pulmonary infarction. Figure 1 illustrates the vegetations on the tricuspid valve, and figure 2 the multiple infarcts in both lower lobes of the lung, which resulted from detachment of thrombi from the tricuspid valve leaflets.

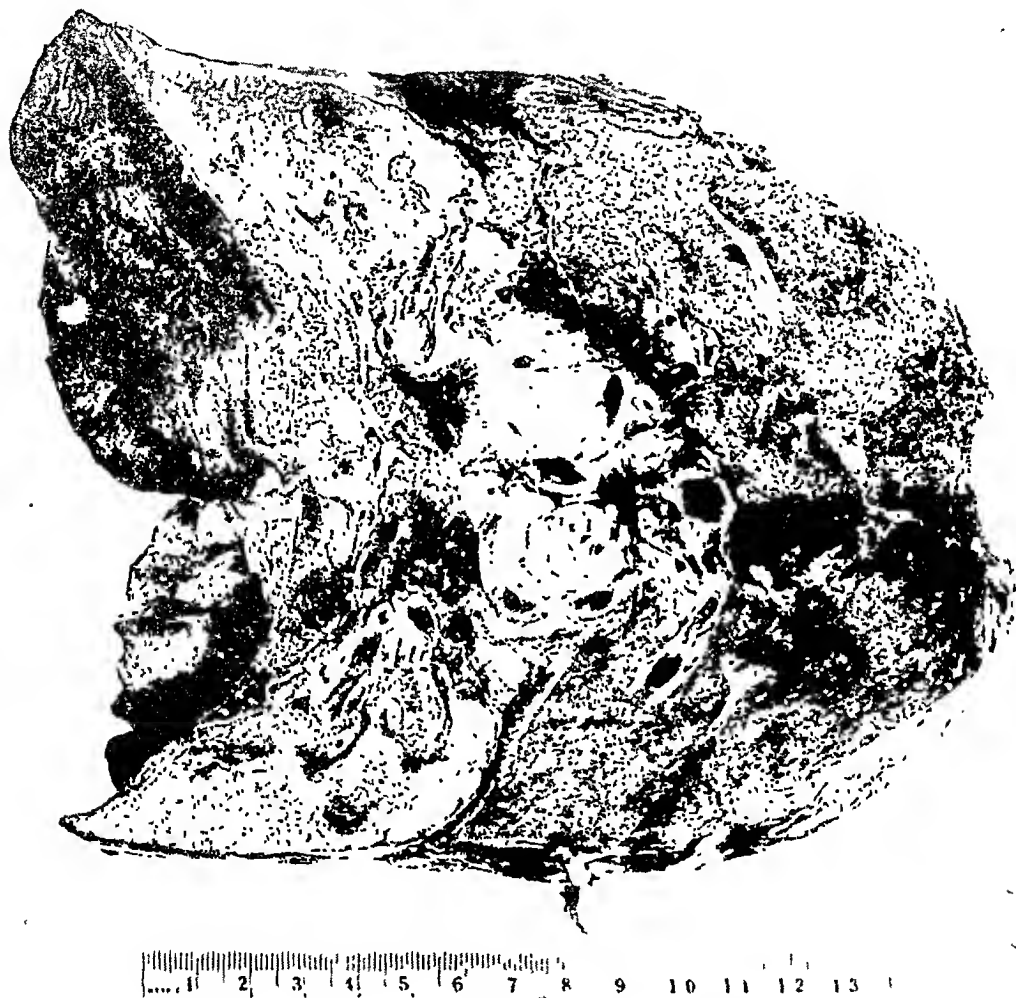


FIG. 2. (Same patient as figure 1.) Note multiple infarcts in both lower lobes of the lung.

A more important form of pulmonary embolism, especially from the standpoint of diagnosis, prophylaxis and treatment, is that type which results from thrombosis in the femoral veins.

The medical profession is deeply indebted to Allen and his associates^{1, 2, 3} who, over the past three years, have emphasized the frequency with which femoral thrombosis occurs postoperatively. They have shown how a simple surgical procedure has been able to reduce significantly the morbidity and mortality from that type of pulmonary embolism which results from thrombosis of the deep veins of the legs.

"Contrary to the previously held belief that almost all instances of sudden postoperative death from pulmonary embolism resulted from a massive thrombus

formed in the pelvic veins, it is now thought that the great majority of these emboli have their origin in thrombosis of the deep veins of the lower extremities. In support of this opinion, Castleman⁴ states that 95 per cent of all emboli exclusive of heart origin can be traced to the leg veins."⁵

Allen accords to Homans the credit for first suggesting that it was feasible to ligate the deep leg veins to prevent pulmonary infarction and embolism.

In 1943 Allen, Linton and Donaldson¹ reported interruption of the femoral vein or veins in 202 patients operated on between 1937 and 1943. Seventy-eight patients had bilateral ligation. There were no deaths and no disabling sequelae in this group.

Allen's most recent contributions^{2,3} present his statistics up to October 1, 1945. He and his associates have performed a total of 1468 femoral vein ligations on 816 patients.

Between 1937 and 1942, bilateral interruption of the femoral veins was performed on 39 per cent of patients operated upon. In 1943 bilateral operations were done in 81 per cent; in 1944, 97.9 per cent, and in 1945 (up to October 1), 98.2 per cent. These statistics are entirely in accord with the expressed opinion of these authors that bilateral operation is desirable even in the absence of clinical evidences of bilateral thrombosis.

In the entire group of 816 patients, the indications for operation were as follows: Leg signs as first symptom, 47 per cent; chest pain as first symptom, 34.4 per cent. No prophylactic interruptions of the femoral veins were done between 1937 and 1942. In 1943, prophylactic ligations comprised 9.2 per cent of those operated upon; in 1944, 25.7 per cent, and in the first nine months of 1945, 36.7 per cent.

It is apparent from these figures that these authors are now convinced of the value of femoral vein interruption in the prevention of pulmonary thrombosis and embolism. Allen³ now advises prophylactic femoral vein interruptions on all patients over 65 years of age prior to operative procedures which prevent early rising.

No fatalities have resulted from 1468 venous interruptions, and there has been only one death from massive embolism following femoral vein ligation. The embolus in this case came from the profunda femoris vein eight days after the superficial femoral had been ligated.

Hamman⁶ states that venous thrombosis is usually unsuspected until pulmonary embolism occurs, and that the signs of femoral thrombosis may appear only after pulmonary embolism has taken place. The pulmonary infarcts are usually multiple and peripheral, and are frequently productive of sterile pleural effusion. When the thrombi are infected, multiple lung abscesses and empyema usually result. The symptoms depend on the size of the vessel occluded. Unless the patient succumbs rapidly to shock from massive embolisms of the pulmonary artery, the usual symptoms are severe pain in the chest, tachycardia, dyspnea, cough, and bloody sputum. The physical signs are fever, râles or frictions, or both, usually over one or both lower lobes, followed shortly by physical signs of consolidation and moderate pleural effusion.

Hamman's observations are almost prophetic when they are compared to the clinical picture of the patient who instigated this report.

Allen and his associates^{1,2} divide femoral thrombosis into two groups,

phlebothrombosis and thrombophlebitis. Phlebothrombosis is a term used by Ochsner and DeBakey⁷ to designate a non-inflammatory lesion. Homans⁸ prefers the term bland thrombosis for the same condition. This type is insidious, in that it may produce no symptoms until pulmonary embolism occurs. It is particularly dangerous because the thrombus, not being tightly adherent to the veins, is easily dislodged. The term thrombophlebitis is used to designate the usual *phlegmasia alba dolens*, which in its fully developed state is characterized by pain and swelling of the affected limb with signs of systemic infection. Embolism is much less likely to occur in these cases, because the thrombus is more likely to be adherent within the inflamed vein.

This brief survey of the etiology of pulmonary embolism, its clinical recognition, and its prophylaxis and treatment, is presented as an introduction to the following case report:

H. L., a white male, age 37 years, was seen in consultation with Dr. Joseph Freeman on May 30, 1945, and admitted immediately to the Hospital of the University of Pennsylvania. His illness began one week previously with fever and pain in the left side of the chest, followed three days later by repeated episodes of frank hemoptysis. On admission, physical examination revealed partial consolidation of both lower lobes, with frictions over the left base. The leukocyte count was 22,400, with 86 per cent of neutrophils. Examination of the sputum revealed no tubercle bacilli on smear, and no pneumococci on culture. Hemolytic streptococci, alpha prime streptococci and *Streptococcus viridans* were present in each of two sputum cultures, on June 4 and 9, respectively.

Roentgen examination of the chest by Dr. E. P. Pendergrass on the day following admission showed bilateral basal consolidation with a small effusion at the left base. It was our opinion that this patient had bronchopneumonia, and he was given sulfadiazine in full doses for six days, with no effect. He was then given 20,000 units of penicillin intramuscularly every three hours for the following 14 days, with no obvious change in his clinical course. On June 12, 550 c.c. of sterile serous fluid were removed from the right chest.

A second roentgen examination by Dr. Robert Barden three weeks after admission still showed bilateral patchy basal consolidation, and an old lesion, presumably tuberculous, at the extreme left apex.

On June 12, the patient suddenly went into profound shock, with marked dyspnea, pallor, and sweating. In view of a dubious previous history of peptic ulcer, hemorrhage from the gastrointestinal tract was suspected, but there was no hematemesis and no melena. He recovered from shock in a few hours. On June 16 the patient complained of slight discomfort in the left calf. Nothing abnormal was found on examination. He was not tested to determine if pain in the calf occurred on dorsiflexion of the foot. When this test is positive, it may, according to Homans, be indicative of thrombosis in the deep veins of the leg. He was discharged from the hospital on July 1, on the sixth afebrile day.

On July 6, coincident with a slight elevation of temperature, he complained of pain in his right chest. Examination on July 23 revealed no abnormal physical signs. At this time the patient had regained eight of the 20 pounds lost during his month's sojourn in the hospital.

During the first week in August there was a recurrence of fever with pain in both sides of the chest. Examination revealed frictions and bilateral patchy consolidation. The fever and pain persisted for 12 days. Roentgen examination by Dr. Barden on August 15 showed a small pleural collection at the left base, with exaggerated lung markings at the site of the previous pneumonic lesions. The lymph nodes in the left hilum were thought to be enlarged.

On November 15, he again developed fever, pain in the right side of the chest, and dyspnea. On November 27 he had repeated bouts of hemoptysis. He was readmitted to the hospital on December 1, 1945, with signs of partial consolidation of both lower lobes, and a small pleural effusion on the right side. Roentgen-ray examination by Dr. Philip Hodes revealed a bronchopneumonic process in the right lower lobe with moderate effusion in the right chest, and a little fluid in the left. Right thoracentesis yielded 280 c.c. of sterile blood-tinged fluid. The laboratory studies were essentially the same as those of the first admission.

On December 11 the patient complained of mild discomfort in the left thigh. His temperature was normal at this time. Examination revealed tenderness and induration over the left saphenous vein. It was not until this time that it was realized that this patient was probably having repeated episodes of pulmonary embolism from thrombosis of the left femoral vein. Surgical consultation with Dr. E. L. Eliason was requested, and he concurred in this opinion. The patient was operated upon by him on December 17, 1945. Because of the operative findings and the extensive surgical procedure which was required, the operative notes by Dr. Robert Welty are quoted verbatim:

"A longitudinal incision was made over the region of the saphenofemoral junction. The saphenous vein was exposed. It was completely occluded by thrombosis and in addition many of its tributaries also were occluded in a similar fashion. The thrombosis extended to involve the femoral vein also. By dissecting upward beneath Poupart's ligament it could be demonstrated that the thrombosis persisted, therefore the incision was extended above Poupart's ligament and by dividing the external oblique it was possible to identify the external iliac at this point. The thrombosis continued to extend so a muscle splitting incision was made dividing the internal oblique and transversalis and reflecting the peritoneum and preperitoneal fat medially. In this way dissection could be carried even farther, but finally a higher muscle splitting incision was necessary in order eventually to identify the most proximal portion of the thrombosis. This was present at the confluence of the external and internal iliac vein. The internal iliac vein was not thrombosed. The external iliac vein was thrombosed up to the point of the confluence and the common iliac was ligated just proximal to this point. The common iliac vein above this point was normal in size and showed no evidence of disease. Prior to ligation it was opened and a retrograde flow of blood was readily obtained with no evidence of a free lying thrombus in this portion of the vein.

"The segment of external iliac and femoral vein was then dissected free down to the point of entrance of the deep femoral vein and this segment was excised. The tributaries were ligated, a single Penrose drain was placed down in the bed from which the vein had been removed and the muscle was closed in layers by interrupted sutures of catgut, the skin being approximated by interrupted vertical mattress sutures of fine steel wire."

Although the operation required almost four hours, the patient's convalescence was entirely uneventful and he was discharged on December 30, 1945, the thirteenth postoperative day.

He had had at least four episodes of pulmonary embolism between April 23 and November 15, 1945. Since operation five months ago, he has remained free of symptoms and in normal health, except for slight residual edema of the left leg, which is not incapacitating him in any way.

Figure 5 is a photograph of the common femoral vein removed at operation, opened to show the extent and magnitude of the thrombus. When the vein was opened it was solidly and completely occluded by thrombus, most of which was not adherent to the inside of the vein. Had this thrombus dislodged in one

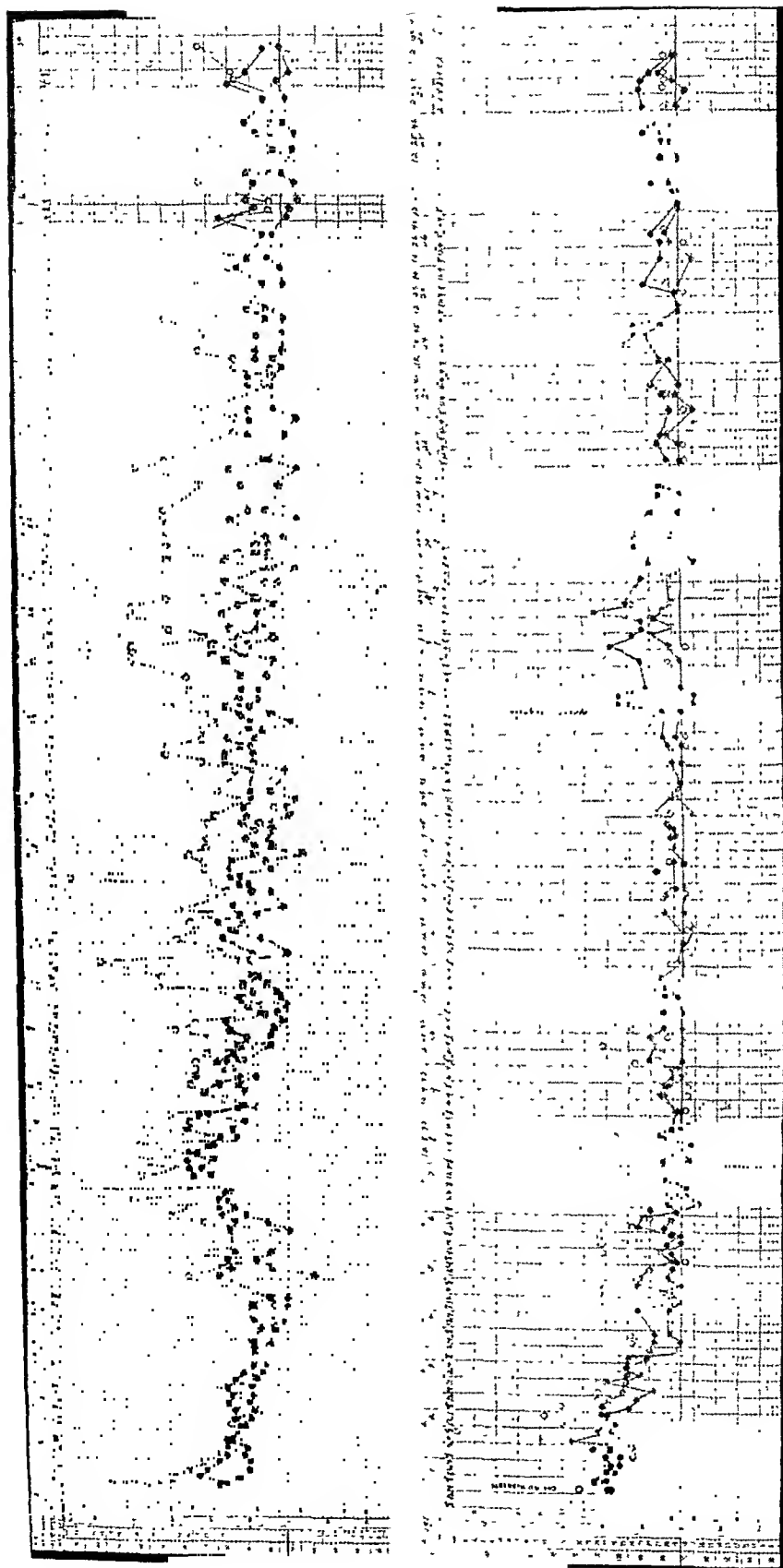


FIG. 3 (*above*). H. L. Clinical chart during first hospital admission, showing severe and prolonged clinical course of pulmonary disease.
 FIG. 4 (*below*). H. L. Clinical chart during second hospital admission. Note normal temperature on December 11, 1945, the day on which femoral thrombosis was found.

piece it certainly was of a size sufficient to occlude the pulmonary artery and produce instant death.

When this patient was first admitted to the hospital, it was thought that he had some form of bronchopneumonia. It soon became apparent that the etiologic agent was not the pneumococcus. Repeated cultures of the sputum failed to reveal any specific organism, and specific therapy, first with sulfadiazine and later with penicillin, was conspicuously futile.



FIG. 5. Common femoral vein removed at operation on H. L. It is opened to demonstrate the extent of the thrombosis. The clear spaces represent areas where the thrombus fell out of the vein when it was opened.

In view of the roentgen finding of a fibrotic lesion in the extreme left apex of the lung and the repeated episodes of frank hemoptysis, the diagnosis of tuberculous bronchopneumonia was entertained, but reasonably excluded by the repeated failure to find tubercle bacilli in the sputum and by the subsequent course of events, characterized by recurring episodes of improvement and relapse. Primary atypical pneumonia was never considered to be a remote possibility, in view of the obvious severity of the infection, the persistent polymorphonuclear leukocytosis and the recurring hemoptysis. The diagnosis of chronic bronchiectasis was seriously entertained, because of the repeated episodes of pulmonary infection and hemoptysis, but there was nothing in the previous medical history, specifically no history of chronic cough or expectoration, to make such a diagnosis tenable.

There was nothing in this patient's previous history which offered an explanation for the femoral thrombosis which was discovered almost seven months after his first episode of pulmonary embolism, and which in retrospect must have been the source of pulmonary infarctions at intervals during all of this time. He had never had either typhoid fever or pneumonia. Either an attack of scarlet fever in childhood, or an insidiously developing thrombophlebitis secondary to a mild long-standing trichophytn infection of the feet, is more intriguing than probable from the standpoint of etiology. Had one been sufficiently alert to the possible presence of bland thrombosis at the time when this patient first complained of slight discomfort in the left calf on the seventeenth day of his first admission, the correct diagnosis might have been reached. Eventually, the demonstrable presence of palpable thrombosis of the left femoral vein led to the correct diagnosis and appropriate operative treatment.

A casual glance at the specimen removed at operation should convince even the most skeptical that its presence constituted an ever-present threat to life.

SUMMARY AND CONCLUSION

Emboli may reach the lungs either from thrombi formed in the right side of the heart, or from those having their origin in the systemic veins, particularly those of the lower extremities. Thrombosis of the leg veins may also result from thrombophlebitis complicating certain infections notably typhoid fever and pneumonia.

Thrombosis of the leg veins occurring postoperatively is a very frequent cause of pulmonary embolism. It is usually possible to prevent this potential catastrophe either by prophylactic bilateral femoral ligation in selected cases, or by prompt interruption of these veins at the first indication of bland thrombosis manifested either locally, or by sublethal episodes of pulmonary infarction and embolism.

The patient whose history is presented in this report had repeated attacks of pulmonary embolism during a consecutive period of almost seven months, and it was only in the last such episode that the correct diagnosis was reached, and then only because slight discomfort in the left thigh led to the discovery of palpable thrombosis in the left femoral vein. No cause for this thrombosis was apparent.

Operative removal of the common femoral vein and its contained thrombus resulted in prompt relief of symptoms. There have been no further episodes of pulmonary embolism since operation five months ago.

This case is reported in order to raise the level of clinical suspicion regarding the presence of bland thrombosis in all instances of atypical pulmonary disease exhibiting those symptoms and physical signs which suggest the possibility of pulmonary embolism.

ADDENDUM

On June 28, 1946, this patient was readmitted to the University of Pennsylvania Hospital with acute thrombophlebitis of the left leg, which responded rapidly and favorably to anticoagulant therapy. On November 13, 1946, he developed cramp-like pain in the right leg, and on the following day he had pain in the chest, cough, fever, and chills. At this time he consulted Dr. Louis A. Soloff, who referred the patient to the Temple University Hospital. He presented signs of consolidation over the right lower lobe posteriorly, and tenderness to deep palpation over both upper legs anteriorly. The diagnosis of phlebothrombosis of the right leg, with pulmonary embolism, was made, and on November 20, 1946, under

spinal anesthesia, the right external and common iliac vessels were exposed by Dr. Burnett, and although no clot was found the common iliac vein was dissected and doubly ligated. The patient's convalescence was complicated by disruption of the wound on November 29, which required secondary suturing. He was discharged on December 12, 1946.

Dr. Freeman, the patient's family physician, reports that up to the present time (December, 1947) there have been no further episodes of phlebothrombosis or pulmonary embolism, and that the patient has remained in normal good health except for considerable edema of the right leg.

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PERIARTERITIS NODOSA WITH RECOVERY: REPORT OF AN UNUSUAL CASE APPARENTLY DUE TO SENSITIVITY TO SULFADIAZINE*

By MORTON J. GOODMAN, M.D., *Portland, Oregon*

PERIARTERITIS nodosa is a disease which is so uniformly fatal that instances of recovery merit special attention. The case herewith recorded is of particular interest because of its association with sensitivity to sulfadiazine, a drug which is now suspected of being antigenic and capable of producing widespread vascular lesions similar to those of periarteritis nodosa.^{1, 2, 3} In addition, the extraordinary and rapid recovery of this patient following the administration of full doses of the offending drug makes the following details worthy of record.

CASE REPORT

J. S., a 17 year old white American student, was admitted to Multnomah Hospital on March 2, 1944 complaining of nose bleeds, sore throat, pains in the joints and back, and a skin rash. He had always enjoyed good health until two and a half months before his admission, at which time he developed a sore throat. He consulted a physician who prescribed sulfadiazine in doses of 15 grains (1.0 gm.) every four hours. The patient took this medication for approximately one week. The sore throat disappeared, and he returned to school feeling quite well. Approximately six weeks later, and one month before his admission to the hospital, he again developed a sore throat. He consulted the same physician who again placed him on sulfadiazine. He

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From the Department of Medicine, University of Oregon Medical School, and the Medical Service of Multnomah Hospital.

took the medication for about two days and then stopped it because it seemed to make him very ill. He promptly developed a skin rash and nose bleeds, became feverish, and felt tired and achy. The rash, at first erythematous, in a few days became purpuric. These symptoms, which began within 24 hours after he started the second course of the drug, persisted and increased progressively in severity until his admission to the hospital four weeks later.

On admission his oral temperature was 99.4° , pulse 100, respirations 30. He looked ill and was in considerable distress. He complained of severe pain in his shoulders, legs and back. A fading purpuric rash was noted over his lower extremities. There was no cyanosis or icterus. His optic fundi were normal. There was a large blood clot in the left nostril and remnants of dark blood were present in the posterior pharynx. His neck was not remarkable. There was no glandular enlargement. The lungs were clear, and the heart was normal in all respects, except for sinus tachycardia and a soft systolic murmur audible at the apex. Blood pressure was 156 mm. of Hg systolic and 92 diastolic. The abdomen was flat and soft. The lower pole of his right kidney was palpable and quite tender. There was marked tenderness in the right costovertebral region. The liver and spleen were not enlarged. Neurological examination revealed all findings within normal limits.

His urine on admission showed specific gravity 1.022, one plus albumin, no sugar, occasional pus cells and occasional red cells in the sediment. The throat culture showed no predominant organism and no hemolytic streptococci. The red cell count was 5,500,000 with 16 gm. of hemoglobin. The white cell count was 10,300 with 60 per cent neutrophils, 3 per cent eosinophils, 10 per cent small lymphocytes, 5 per cent monocytes and 4 per cent staff cells. The sedimentation rate was 3 in 15 minutes, 22 in 45 minutes (Westergren). The platelet count was 76,000; blood urea nitrogen was 14 mg. per cent.

He was given salicylates and codeine for pain and sodium pentobarbital for rest. Two days after his admission to the hospital his back pain became extremely severe. His blood pressure rose to 164/104. His pain was most intense in the neighborhood of the right costovertebral angle and seemed to radiate into the right flank. A large number of red cells appeared in his urine. Salicylates were stopped. The prothrombin time was 39 per cent of normal. He was placed on parenteral menadione, and two days later the prothrombin time had risen to 66 per cent of normal. Bleeding and coagulation times were within normal limits. Four days after admission he began to vomit, and for the next five weeks he retained very little food or fluid. His nutrition and his fluid and electrolyte balance were maintained largely by the intravenous route. He lost weight rapidly. His temperature ranged from 99.5° to 103° each day. His generalized muscle aches and pains became more intense.

On March 9, one week after admission to the hospital, he developed an acute epididymitis. He displayed migratory painful swelling of both shoulders and of his left elbow. His sore throat was very troublesome and interfered with his taking nourishment and fluids, and he vomited a great deal. On March 15, two weeks after admission, a biopsy of his left deltoid muscle was performed. The pathologic diagnosis was periarteritis nodosa (figure 1). The patient became very apprehensive and panicky, and his ever present fear of death complicated his nursing care. Red cells, albumin, and a few casts were present in the sediment of each of many urine specimens. He occasionally had gross hematuria. Hemoglobin ranged from 16.2 gm. to 14.4 gm., and red cells from 5.4 million to 4.0 million. The white cell count ranged from 10,300 to 19,900 and the polymorphonuclear neutrophile count ranged from 67 to 81 per cent. Three eosinophils were recorded on one blood smear, and no eosinophils on 17 other smears. The sedimentation rate remained quite rapid, and the platelet count varied from 76,000 to 147,000. Several electrocardiograms showed nothing but sinus tachycardia. One tracing showed depression of the ST segments in Leads I and II and

slurred QRS complexes. These findings were interpreted as evidence of an active myocardial process. The sternal marrow was aspirated on March 13 and showed an essentially normal cellular pattern, except for the myelocyte count which was at the upper limit of normal. Blood cultures, and serum agglutination tests for the typhoid-

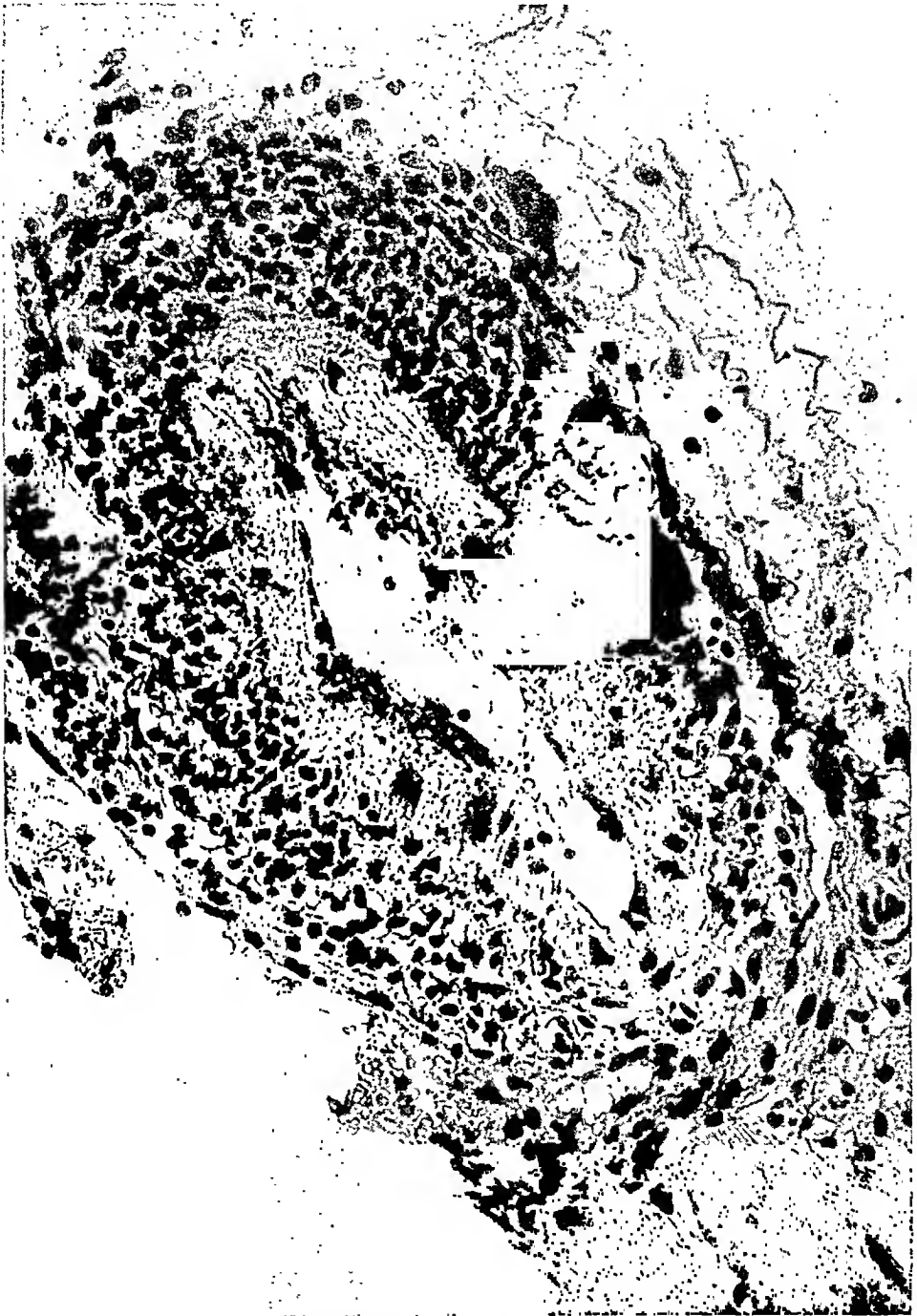


FIG. 1. A small artery in the deltoid muscle showing inflammation and hyaline degenerative changes in the outer vessel wall. The outer coats and the perivascular area are infiltrated with round cells and polymorphonuclear leukocytes. The dark patch on the vessel is an artefact.

paratyphoid group and for *Brucella abortus*, were all negative. The Paul-Brunnell test was negative in a 1-4 dilution. A flat film of the abdomen taken on March 8 showed the right kidney shadow to be obscured. The left kidney appeared normal and no opaque calculi were seen.

On April 7, five weeks after his admission, his condition was desperate and it seemed as though he would soon die. On this date a house physician, apparently unfamiliar with the patient's history of sulfonamide sensitivity, resumed therapy with sulfadiazine! The patient was given one gram of the drug orally. Within 30 minutes he developed a generalized urticarial rash on his trunk and extremities, which responded to hypodermic epinephrine. The sulfadiazine was continued, one gram every four hours for five days. During this time, the patient had numerous urticarial eruptions which were controlled by repeated injections of epinephrine. On April 12, sulfadiazine was discontinued.

On April 14 he began to improve. He was able to retain all of his food. His temperature dropped appreciably to a daily peak of 99.5° and by April 16 it was normal and remained so. On April 19 he was able to sit in a wheel chair. He continued to show daily improvement and gained strength rapidly. The urine abnormalities cleared, and his pain subsided. He was discharged from the hospital on April 27. By June 15, 1944 he was able to enroll in summer school. He has been studied at frequent intervals since that time, and his examinations have all been completely negative. His blood pressure and urine have shown no abnormalities. In March, 1945, one year after the onset of his illness, he passed the Selective Service Examination. He was ultimately rejected by the Medical Board on the basis of his history. He was last thoroughly checked in August, 1946, 28 months after his recovery and was found to be in splendid health. He stated that he had not had a sick day since leaving the hospital.

On May 15, 1946, approximately two years after his recovery, an intradermal test for sulfonamide sensitivity was done, according to the technic described by Leftwich⁴: 0.1 c.c. of serum collected from an individual with a therapeutic blood sulfadiazine level, and 0.1 c.c. of control serum from the same individual without the drug were injected intradermally into the forearm of the patient. The sulfonamized serum produced a wheal of 13 mm. in 20 minutes; the control wheal was 12 mm. The test indicated no demonstrable sulfadiazine sensitivity. On August 6, 1946, .12 gm. (2 grains) of sulfadiazine was administered orally to the patient, and no reaction whatever was noted. A trial with full therapeutic doses of the drug was proposed, but the patient, recalling his previous experience, refused the test.

Since Kussmaul and Maier⁵ first described periarteritis nodosa in 1866, reports of over 400 cases of the malady have appeared in the medical literature. The disease is usually first recognized at necropsy, but recently many cases have been confirmed antemortem by biopsy. An occasional case showing recovery or an unusually long remission has been recorded.⁶

Much attention has been directed in recent years to the striking similarity of the lesions and clinical features of periarteritis nodosa and those of anaphylactic reactions. The hypothesis of vascular allergy has been postulated by many observers⁷ as the cause of the various phenomena present in this disease. Gruber⁸ in 1923 suggested that periarteritis nodosa was a hypersensitization phenomenon involving the arterial walls and occurring during the course of the prolonged infection. Many other observers⁹ have emphasized the frequency with which the disorder is associated with allergic phenomena, particularly asthma. Wilson and Alexander¹⁰ checked the protocols of 300 consecutive cases of periarteritis nodosa reported in the literature and found bronchial asthma in 18 per

cent. These observers also emphasize that in many of the cases in which differential blood counts are recorded hypereosinophilia was present. Cohen, Kline, and Young¹¹ contend that periarteritis nodosa is a manifestation of clinical allergy of so severe a degree that irreversible destructive lesions occur in blood vessels. The milder vascular allergic reactions they feel, disappear without permanent tissue change; the more severe reactions are associated with tissue necrosis and are irreversible. Harkavy¹² presents a similar thesis and postulates that varying degrees of hyperergic vascular response determine the extent, and degree and reversibility of the lesions in the shock tissues affected.

In most instances bacterial allergies seem to be implicated, but Rich^{1, 2, 3} has recently drawn attention to the possible rôle of other antigens which may produce such vascular lesions. He noted the widespread typical lesions of periarteritis nodosa in the viscera of necropsy cases in which there were definite histories of hypersensitivity to serum or to sulfonamides shortly before death. Furthermore, he was able to reproduce these lesions in rabbits following injections of large amounts of foreign serum. He was unable to sensitize his animals to sulfonamides because the drug apparently does not combine with plasma protein of rabbits to form a new molecule which is antigenic. However, Rich suggests that in humans sulfonamide drugs may be the inciting antigen and produce widespread vascular disease. He points out that there has been a marked increase in the number of cases of periarteritis nodosa coming to autopsy at the Johns Hopkins Hospital since the introduction of sulfonamides in 1936. He emphasizes the importance of a careful search for the inciting antigen in all cases of periarteritis nodosa that come under clinical observation. Labby and McDermott¹³ have performed biopsies of muscles underlying the skin lesions produced by sulfonamide sensitivity and have found perivascular inflammatory lesions similar to the lesions of periarteritis nodosa.

In the case here reported, the relationship between the ingestion of the sulfonamide and the onset of the patient's illness seems more than coincidental. The initial dose of sulfadiazine was apparently the sensitizing dose. When the drug was again taken six weeks later the patient immediately became very ill and developed fever, a skin rash and other phenomena indicative of drug sensitivity. These symptoms did not subside but progressed rapidly to the fulminating illness described. A picture of widespread vascular injury was suggested by the nephropathy with hematuria and hypertension, the generalized muscle tenderness, the hemorrhagic phenomena involving the skin and mucous membranes, and the electrocardiographic evidence of myocardial damage. A diagnosis of periarteritis nodosa was established by biopsy. An extraordinary situation arose at the height of the patient's illness when he was given full doses of sulfadiazine and in spite of obvious sensitivity, the drug was continued for five days. Even more striking was the fact that the patient began to improve shortly after sulfadiazine was stopped. It is possible that coincidence alone explains the apparent striking therapeutic paradox of prompt recovery following the administration of an obviously noxious antigen. It is likewise possible that the sulfadiazine may have controlled an infectious agent to which the patient had become sensitive. Sulfonamides have had a fair and unsuccessful trial in the treatment of many cases of periarteritis nodosa and only one instance of apparent recovery after its use had been reported.¹⁴ In the present case one might

speculate that the patient may have been desensitized by means of overloading with specific antigen. Urbach¹⁵ quotes certain experiments of Besredka in which animals which had sustained macroshock type of anaphylactic reactions were reinjected after a short period of time with a multiple of the lethal dose of the antigen. The animals were found to be completely insensitive. Urbach¹⁶ further states that "deallergization by means of antigen overloading" succeeds under certain circumstances when the reinjection dose brings on a severe anaphylactic shock that is not immediately fatal but is followed by death after one or two hours, or by ultimate survival of the animal after severe prolonged manifestations. He demonstrated by perfusion experiments that the organs of an animal thus exposed to long lasting shock may become deallergized for the duration of its life with the inhibition of the antigen-antibody reaction.

In the patient herein reported one might hypothesize on the basis of such experimental work that some type of satiation of antibodies occurred in the primary shock tissues. The result was clinical insensitiveness to the antigen which had been given in doses sufficient to produce a prolonged severe non-lethal anaphylactic vascular reaction.

SUMMARY

1. A case of periarteritis nodosa with recovery is reported associated with and apparently caused by sensitization to sulfadiazine.

2. Prompt recovery seemed to follow a severe prolonged anaphylactic reaction produced by the unwitting administration of the drug at the height of the patient's illness.

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CHRONIC LEAD POISONING AND HYPERTENSION, WITH DEATH RESULTING FROM PERITONITIS; REPORT OF A CASE

By JOHN Q. GRIFFITH, JR., M.D., F.A.C.P., and RALPH JONES, M.D.,
Philadelphia, Pennsylvania

FOUTS and Page¹ were unable to produce arterial hypertension in two dogs poisoned with lead, and expressed doubt that lead was ever a cause of hypertension in man. Griffith and Lindauer,² however, were able to produce arterial hypertension in rats chronically poisoned with lead and this has been confirmed by Diaz-Rivera and Horn.³ In the case here reported it is believed that chronic lead poisoning offers the best explanation for both the hypertension and the final fatal outcome.

CASE REPORT

On February 16, 1943, a white girl, 20 years of age, was admitted to the medical ward of the Hospital of the University of Pennsylvania on the service of Dr. O. H. Perry Pepper. At that time her blood pressure was 240 mm. Hg systolic and 166 diastolic and she was blind. She had been previously admitted to two other hospitals.

Her history began at the age of 15 when, after participating in a game of basket-

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From the Robinette Foundation and the Medical Clinic of the Hospital of the University of Pennsylvania.

ball, she developed weakness and palpitation. This soon passed off but it was found at that time that her systolic blood pressure was 160. Six months later she was admitted to the first hospital, where it was found her blood pressure was 160/120, her heart was normal in size as shown by orthodiagram, electrocardiogram was normal, and ophthalmoscopic examination revealed only slight narrowing of the arteries. One year later she was readmitted to the first hospital. Blood pressure on admission was 170/130, but thereafter it varied from 150/110 to 200/156. Orthodiagram at that time revealed a heart larger than normal, but the electrocardiogram was still normal. Renal studies were again negative except for a few casts and white cells in the urine. Ophthalmoscopic examination this time showed narrow vessels and rather hazy disc margins. At that time therapy with potassium thiocyanate was begun, without improvement. It was being continued, however, when she was re-admitted one year later. This time systolic blood pressure ranged between 170 and 200 mm. of mercury, but diastolic pressure was fairly constant at about 150 mm. Ophthalmoscopic examination was reported as showing arteries definitely reduced in caliber, papilledema of 1 or 2 diopters, and a few fresh hemorrhages. Renal studies were still normal, and she was continued on thiocyanate. About that time (1940) she entered college, where she continued until 1942, with little complaint except occasional blurring of vision.

In September, 1942, she was admitted to the second hospital. Blood pressure was 220/175, her heart was enlarged. Ophthalmoscopic examination was said to show papilledema of 2 to 4 diopters, narrow arteries, and fresh hemorrhages and exudates. Renal studies were still satisfactory, the urea clearance showing 195 per cent of average normal function. A muscle biopsy from the gastrocnemius was reported to show arteriolar sclerosis. On October 13, 1942, bilateral lumbar sympathectomy and celiac ganglionectomy were performed. There was an immediate drop in blood pressure to 140/100, but within a few days it rose again to 220/160. On the fifth day post-operatively her vision began to fail, and within 48 hours she could distinguish only light and dark. Otherwise she felt reasonably well until three weeks prior to admission to the University Hospital, when she developed persistent diarrhea and loss of weight.

Upon admission, an unusual eye ground picture was described by Dr. Francis H. Adler, as follows: "The disc is definitely pale and the outlines are irregular and partly obscured by changes which probably represent coagulation necrosis and not simple edema. Throughout the whole posterior pole are hard white deposits. These are probably lipid in nature. There are no cotton patches present and no hemorrhages. The arteries are very markedly reduced in size and many of the secondary branches have entirely disappeared. The whole picture is of endarteritis with occlusion of the central artery: it is not that of malignant hypertension. I doubt if this girl ever had a true papilledema. Diagnosis: The end stages of extreme endarteritis obliterans of the retinal arteries."

This report suggested to us the possibility of lead poisoning, and further studies were made along this line. Additional history revealed that the patient had spent all her life, except when away at school, living in a remodeled farmhouse with a water supply obtained directly from an adjacent well. The piping originally installed was entirely composed of lead, but one year before the patient's birth this was changed to iron piping, it was said, although it seemed fairly certain that the portion of pipe passing through the foundations and actually entering the house remained the original lead. The patient's grandmother had lived in this house and drunk this water for 50 years without harm, although some of this period undoubtedly predated the installation of the plumbing. However, her father had died before the age of 50 of "acute indigestion" and her mother had died before the age of 50 with Bright's disease and hypertension. She had two brothers, aged 18 and 19 years, who were known to have blood pressures, respectively, as high as 180 and 150 systolic. Examination of the patient's

blood showed basophilic stippling, to the extent of 2 per cent, and the blood of one brother, the only one who could be reached, also showed basophilic stippling. Examination of the patient's blood for lead showed 0.070 mg. of lead per 100 gm. of blood in sample A, and 0.070 mg. in sample B. By the method used⁴ the average normal figure (i.e. for subjects not poisoned by lead nor exposed beyond casual daily contacts) is 0.030 mg. of lead per 100 gm. of blood, and only one of a series of 73 normal subjects exceeded 0.050 mg. Roentgen-ray of bones did not show any changes attributable to lead.

Other studies included a blood urea nitrogen of 17 mg. per cent and a urea clearance of 50 per cent average normal function. Urinalysis showed abundant albumin, hyaline casts and white cells. Gastric acidity was normal. Gastrointestinal series showed abnormal motility with an increased rate of emptying of the lower ileum, and granular thickening of the walls of the cecum and ascending colon. Stool examination showed no parasites.

Her course was progressively downward. One month after admission fluid was found in the left chest and removed by thoracentesis. Vomiting and diarrhea became intractable and were the eventual cause of death which occurred on May 5, 1943.

Necropsy was performed 12 hours after death. Multiple ulcerations were found in the ileum, one of which had ruptured with resulting peritonitis, and this was thought to be the immediate cause of death. The lungs showed passive congestion and edema. The kidneys were grossly normal, but microscopically they showed changes indicative of nephrosclerosis.

COMMENT

Unusual features include: (1) The height of the blood pressure as compared with the relatively few symptoms attributable to it. (2) Blindness occurring following sympathectomy, and the unusual eye grounds. (3) The terminal picture with enteritis and peritonitis. (4) The elevated level of blood lead, the basophilic stippling, the history of possible source of lead poisoning and the family history.

It seems to us that lead poisoning is a possible explanation for the entire picture, and the only single explanation that can be offered. Fishberg⁵ describes cases where blindness has occurred in acute lead poisoning, where the blindness is thought to be due to spasm of the retinal arteries with occlusion. While our patient was certainly not an example of acute lead poisoning, the increased blood lead concentration definitely establishes exposure to lead considerably in excess of that usually found. This exposure, extending from the pre-natal period through childhood, may well have left the patient vulnerable to crises such as that resulting from the sympathectomy, accompanied by acidosis or other profound metabolic disturbance. Sudden mobilization of lead is known to result from acidosis and other disturbances of homeostasis. Sympathectomy has been shown by McGrath⁶ and later by Griffith, Comroe and Zinn⁷ to increase greatly the susceptibility of blood vessels in animals poisoned with ergotamine tartrate, a poison also capable of producing endarteritis obliterans. It is possible that a sympathectomized area may also be more vulnerable to lead, and that this may account for the unusual severity of the enteritis, presumably due to lead, following the sympathectomy.

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EDITORIAL

A NEW RICKETTSIAL DISEASE

DURING the year 1946 many cases of an acute febrile infection of unusual character were observed in New York City.^{1, 2} Most of these cases occurred in a group of apartment houses in a small area in Regency Park (Borough of Queens) housing 543 families, although similar cases were subsequently reported from three other boroughs. The clinical picture was so characteristic and the etiological features so interesting that the disease merits some attention.

The onset in most cases was abrupt with malaise, fever, usually chills and sweats, headache, pain in the orbits, and severe aching in the back and muscles which are reminiscent of a severe influenzal infection.

In about two-thirds of the cases the patients had noticed a localized cutaneous lesion several days before the onset of the fever. This was described as a pimple, boil or insect bite, although none had observed the biting. The lesion started as a small firm papule which gradually enlarged (0.5 to 1.5 cm. or more in diameter) and became vesicular; later there was central necrosis with the formation of a blackish eschar, but there was virtually no local pain or tenderness. Some erythema appeared in the skin about the lesion, and as a rule there was some enlargement of the regional lymph nodes but no obvious lymphangitis. This lesion healed in the course of about three weeks. It might be found on almost any part of the body but was usually on a covered portion. This premonitory initial lesion appears to be a virtually constant feature since it was found when searched for in nearly every patient who was observed during the active stage of the infection.

Either coincident with the onset of the fever or usually within 48 hours after this, a rash appeared. This consisted of a limited number (five to 100 or more, usually 20 to 40) of small, discrete, firm, erythematous papules somewhat resembling the initial lesion but with a diameter only one-half to one-third as great. Within a day or two in most cases a small firm vesicle appeared in the apex of the papule. Later this dried, often a small eschar formed, and after about four to seven days it healed without scarring. There was no itching or discomfort. The rash had no characteristic distribution except that it did not appear on the palms and soles and rarely on the mucous membranes.

The fever was typically remittent, the temperature often reaching 103° to 104° F., and it was accompanied by marked lassitude or prostration. It fell by lysis after an average duration of about one week, and all patients recovered without complications or sequelae. Except for occasional anor-

¹ SUSSMAN, L. N.: Kew Gardens' spotted fever, *New York Med.*, 1946, ii, 27-28 (August 5).

² SHANKMAN, B.: Report on an outbreak of endemic febrile illness, not yet identified, occurring in New York City, *New York State Jr. Med.*, 1946, xvi, 2156-2159.

exia or nausea, gastrointestinal disturbances were rare, and no patient showed any significant respiratory symptoms.

There was generally a moderate granulocytopenia, but otherwise the usual laboratory examinations showed nothing significant. In particular there was no agglutination of Proteus OX19, OX2 or OXK (except feeble reactions in a few cases).

Because of a slight resemblance to chickenpox, for which some of the cases had been mistaken, the name "rickettsialpox" was proposed by Greenberg et al.,³ who have published an excellent description of the disease. Although the character of the eruption justifies the use of the term, pox, the resemblance to chickenpox is really superficial, and a clinical differentiation should usually be simple.

Studies carried out at the National Institute of Health in coöperation with the New York City Department of Health have revealed the agent causing the infection and important evidence regarding its transmission. By intraperitoneal inoculation of mice with blood obtained in the acute stage of the disease, Huebner et al.⁴ isolated from each of two patients an organism which proved to be a rickettsia. This was maintained by serial passages in mice and guinea pigs, and in the latter species it excited an inflammatory reaction of the scrotum somewhat resembling that caused by the rickettsia of endemic typhus. It also grew luxuriantly in the yolk sac of fertile eggs, causing death of the embryos, but it could not be cultivated in any ordinary (lifeless) culture media.

These investigators prepared an antigen from the yolk sac cultures by the method of Topping and Shepard and utilized this for complement fixation tests by the Bengtson method with the serum of convalescent patients and of guinea pigs which survived infection. In all the cases reported a positive reaction was obtained, and in the four cases in which a comparison was possible, the serum during convalescence showed a much higher titer than that obtained during the early stage of the disease.

By making "cross tests" with immune serum and antigens similarly prepared from other species of rickettsia, they showed that this strain was antigenically distinct from the agents causing endemic typhus fever, tsutsugamushi (scrub typhus) and Q fever. There was, however, a rather marked cross reaction with the antigen of Rocky Mountain spotted fever. They regard the organism as a distinct species and proposed for it the name *Rickettsia akari*.

Investigation of the premises in which some of these cases occurred showed that mice were numerous and that the basements were heavily infested with the rodent mite *Allodermamyssus sanguineus*. This observation and the fact that no other vermin was found suggested that the urine and the

³ GREENBERG, M., PELLITERI, O., KLEIN, I. F., and HUEBNER, R. J.: Rickettsialpox, Jr. Am. Med. Assoc., 1947, cxxxiii, 901-906.

⁴ HUEBNER, R. J., STAMPS, P., and ARMSTRONG, C.: Rickettsialpox—a newly recognized rickettsial disease. I. Isolation of the etiological agent, Pub. Health Rep., 1946, lxi, 1605-1614.

mites might constitute respectively the reservoir and the vector of the infection. Huebner et al.⁵ succeeded in isolating from these mites two strains of rickettsiae which were identical in morphology, pathogenicity and antigenic properties with the human strains. One was obtained from a guinea pig which had received an intraperitoneal injection of ground-up mites and the other from a young mouse on which mites had been allowed to engorge. Huebner et al.⁶ also isolated a similar strain from a mouse which was trapped on the premises. One of the investigators who had collected and processed the mites developed a typical attack of the disease three weeks later. The evidence is, therefore, strong that the infection was native in the mice and that it was conveyed from mouse to mouse and from mouse to man by these mites.

Further observation will be required to determine the practical importance of the infection and its precise relation to other rickettsial diseases. Nothing is known as to the distribution of the infection among mice. It appears to have been prevalent among mice at the location of the epidemic, since mice trapped there were mostly refractory to inoculation, and four of seven mice tested gave positive complement fixation reactions. Laboratory white mice and house mice trapped in Virginia, on the other hand, were usually susceptible to inoculation and gave negative serum reactions.

Little is known as to the distribution of the vector. Muesebeck is quoted⁷ as stating that specimens of this mite have been collected from Tucson, Ariz., Indianapolis, District of Columbia, New York City, Philadelphia and Boston. It seems likely, therefore, that it may be found widely distributed if a systematic search is made.

The disease resembles tsutsugamushi in having a mite as a vector and in showing an eschar at the site of the bite. The latter infection, however, is a severe one with a high mortality, and the agents are antigenically distinct. The rash of rickettsialpox is also radically different, as it is, indeed, from that of all other known rickettsial infections. *Rickettsia akari* seems to be closely related antigenically to *R. rickettsiae* of Rocky Mountain spotted fever. The latter, however, is a severe infection with a high mortality, there is no local eschar, and the rash is quite different.

This infection seems to resemble most closely the fièvre boutonneuse of the Mediterranean region, the agent of which is named *R. conori*. This is likewise a mild infection, and there is usually a local eschar, although the vector is reported to be a tick and the reservoir of infection the dog. No direct comparison of these organisms as to their antigenic relationships has been published, but as *R. conori* has been reported⁷ to show complete cross

⁵ HUEBNER, R. J., JELLISON, W. L., and POMERANTZ, C.: Rickettsialpox—a newly recognized rickettsial disease. IV. Isolation of a rickettsia apparently identical with the causative agent of rickettsialpox from *Allodermanyssus sanguineus*, a rodent mite, Pub. Health Rep., 1946, lxi, 1677–1682.

⁶ HUEBNER, R. J., JELLISON, W. L., and ARMSTRONG, C.: Rickettsialpox—a newly discovered rickettsial disease. V. Recovery of *Rickettsia akari* from a house mouse (*Mus musculus*), Pub. Health Rep., 1947, lxii, 777–780.

⁷ BADGER, L. F.: Rocky Mountain spotted fever and boutonneuse fever, a study of their immunological relationships, Pub. Health Rep., 1933, xlviii, 507–511.

immunity with *R. rickettsiae*, it seems probable that it is also related to *R. akari*. Such relationships suggest that these three species may be relatively recent variants of a common ancestor. Caminopetros (1932) has described scrotal reactions in guinea pigs infected with *R. conori* which seem to resemble those caused by *R. akari*. There appear, however, to be differences in the pathogenicity of the two rickettsiae for other animals; the cutaneous eruptions they produce in man are different; and *R. conori* excites the production of agglutinins for strains of *Proteus* X,⁸ whereas *R. akari* does not. The investigators, therefore, seem justified in regarding *R. akari* as a distinct species.

If this epidemic proves to be merely an unusual and fortuitous transfer of a rodent infection to man, it is, perhaps, primarily a matter of scientific interest. If, however, it proves to be widely distributed, even though mild and sporadic in occurrence, like endemic typhus, it becomes a problem of immediate practical importance. This point might be settled simply, by a search for cases of the disease. The clinical manifestations are so distinctive that it should be recognized easily if the observer is familiar with it. One not familiar might well ignore sporadic cases of so mild an infection, dismissing them as "atypical chickenpox" or as a "skin rash" of minor importance. It is stated⁶ that some of the mites of this species, collected in other localities, had been taken on man, and were noted as "causing rash." It is, indeed, probable that the nature of the disease in New York City would not have been discovered if it had not occurred in epidemic form.

P. W. C.

⁸ DURAND, P.: La reaction de Weil-Félix dans le fièvre boutonneuse, Arch. Inst. Pasteur de Tunis, 1932, xx, 395-421.

REVIEWS

Rh: Its Relation to Congenital Hemolytic Disease and to Intragroup Transfusion Reactions. By EDITH L. POTTER, M.D., Ph.D., Asst. Prof. of Pathology, Department of Obstetrics and Gynecology, The University of Chicago and The Chicago Lying-In Hospital. 344 pages; 14.5 × 21 cm. The Year Book Publishers, Inc., Chicago, Illinois. 1947. Price, \$5.50.

Dr. Potter has performed a great service for the medical profession in preparing this monograph on the Rh factor. In the seven years since its discovery by Landsteiner and Weiner, a tremendous literature has developed as evidenced by the bibliography of over 700 references cited by the author. The material presented is discussed with authority based upon the author's personal experiences as well as upon careful analysis of the literature. In spite of the fact that many aspects of the subject are still in a state of flux, as the author points out, a sufficient bedrock of permanent data has now been established which is of importance to anyone concerned with blood transfusion therapy, or the care of the pregnant woman and her infant in the neo-natal period. Historical and technical material is exhaustively covered and there is an admirable consideration of the pathology of congenital hemolytic disease. The reviewer, incidentally, is entirely in sympathy with the use of the term congenital hemolytic disease as opposed to the less descriptive and often misused term, erythroblastosis fetalis. The publishers have provided a pleasing format. The book is highly recommended to those seeking a general acquaintance with the subject, as well as to those more specifically interested in the field.

M. S. S.

If You Ask My Advice: Frank Discussions of Family Problems. By HENRY PLEASANTS, JR., M.D. 110 pages; 21 × 14 cm. 1946. Bruce Humphries, Inc., Boston. 1946. Price, \$2.00.

This book is a short one designed to give advice to lay people on a number of topics related to psychiatry, with chapter headings such as: Insanity in the Family, The Problem Child, Child Discipline, The Alcoholic, The Drug Addict. As is usual when books are written on specialized scientific topics by persons with little or no knowledge of the topic, there is a generous sprinkling of misinformation. This book is no exception. This reviewer could not recommend this book to anyone either lay or professional.

H. W. N.

Developmental Diagnosis: Normal and Abnormal Child Development—Clinical Methods and Pediatric Applications. (2nd Edition, Revised and Enlarged.) By ARNOLD GESELL, M.D., and CATHERINE S. AMATRUDA, M.D. 496 pages; 24 × 16 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1947. Price, \$7.50.

In this effective revision of the first edition, the authors have enlarged both the extent and depth of the material contents. Case examples, drawn from the Yale Clinic of Child Development, are provided illustrative of the many diagnostic problems discussed. The first part of the volume deals with basic principles of child development, behavior characteristics and their growth patterns from four weeks to three years. Norms of development, photo tracings along with developmental tests are provided to strengthen the practical value of the volume. The second section of the volume deals with deviates from the authors' norms of normal development. The

problem of amentia is discussed at great lengths, both etiologically and symptomatologically, followed by the possible effects of these defects on performance, total development and overall personality pattern. Included are two chapters concerning the neurological aspects of infant development along with effects of cerebral injuries. The third section of the volume discusses the rôle of private medical and public health in guarding the growth of the early child. The volume is completed with six appendices summarizing the examination technic, charts of growth trends, equipment lists, use of cinema equipment, and suggested readings. The volume will be of interest to those in close contact with the young child, both as a textbook and handy reference.

H. W. N.

The Clinical Examination of the Nervous System. 8th Ed. By G. H. MONRAD-KROHN, M.D., F.R.C.P., Professor of Medicine in the Royal Frederick University, Oslo, etc. 380 pages; 13 × 19 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers. 1947. Price, \$4.50.

This eighth edition has been revised and improved. It is written for medical students so that they may learn to perform an orderly and comprehensive neurological examination. It covers the nervous system in a brief but adequate manner. The photographs are well done to illustrate various lesions and the diagrams are well placed. The roentgenograms and arteriograms are exceptionally well reproduced.

No attempt is made to correlate and interpret the neurological findings. Neurological diseases are not discussed. The student will find this book a very valuable adjunct to his library. It is a ready reference book.

W. L. F.

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Blood Derivatives and Substitutes: Preparation, Storage, Administration and Clinical Results Including a Discussion of Shock: Etiology, Physiology, Pathology and Management. By CHARLES STANLEY WHITE, M.D., ScD., Former Professor of Surgery, George Washington University School of Medicine, etc., and JACOB JOSEPH WEINSTEIN, B.S., M.D., Associate in Surgery, School of Medicine, George Washington University. 484 pages; 23.5 × 16.5 cm. The Williams & Wilkins Company, Baltimore. 1947. Price, \$7.50.

Conference on Metabolic Aspects of Convalescence: Transactions of the Thirteenth Meeting. Edited by EDWARD C. REIFENSTEIN, JR., M.D., Massachusetts General Hospital, Boston. 232 pages; 23 × 15 cm. (paper-bound). Conference sponsored by Josiah Macy, Jr., Foundation, New York. 1946. Price, \$2.00.

Conference on Metabolic Aspects of Convalescence: Transactions of the Fourteenth Meeting. Edited by EDWARD C. REIFENSTEIN, JR., M.D., Sloan-Kettering Institute, New York. 190 pages; 23 × 15 cm. (paper-bound). Conference sponsored by Josiah Macy, Jr., Foundation, New York. 1946. Price, \$2.25.

Differentialdiagnose der Lungenrontgenbilder: Besondere Berücksichtigung derjenigen Erkrankungen die mit der Lungentuberkulose verwechselt werden können. By DR. MED. RUDOLPH ZEERLEDER. 296 pages; 24 × 16 cm. Medizinischer Verlag Hans Huber, Bern. 1947. Price, fr. 28.

- Diseases of the Nervous System.* 3rd Ed. By W. RUSSELL BRAIN, D.M. (Oxon.), F.R.C.P. (London), Physician to the London Hospital, etc. 987 pages; 22 × 14.5 cm. Oxford University Press, New York. 1947. Price, \$10.75.
- Diseases of the Nose, Throat and Ear.* 9th Ed., Revised. By WILLIAM LINCOLN BALLENGER, M.D., F.A.C.S., Late Professor, School of Medicine, University of Illinois; and HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Associate Professor and Acting Chairman of the Department of Otolaryngology, Northwestern University School of Medicine, Chicago, etc.; assisted by JOHN JACOB BALLENGER, B.S., M.D., Research Fellow in Otolaryngology, Northwestern University School of Medicine, Chicago. 993 pages; 24 × 16 cm. Lea & Febiger, Philadelphia. 1947. Price, \$12.50.
- The Foot and Ankle: Their Injuries, Diseases, Deformities and Disabilities.* 3rd Ed., Revised. By PHILIP LEWIN, M.D., F.A.C.S.; Associate Professor of Bone and Joint Surgery, and Acting Head of Department, Northwestern University Medical School, etc. 847 pages; 24 × 16 cm. Lea & Febiger, Philadelphia. 1947. Price, \$11.00.
- History of Medicine: A Correlative Text, Arranged According to Subjects.* By CECILIA C. METTLER, A.B., Ed.B., A.M., Ph.D., Late Assistant Professor of Medical History, Univ. of Georgia, School of Medicine, etc.; edited by FRED A. METTLER, A.M., M.D., Ph.D., Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. 1215 pages; 24 × 16 cm. The Blakiston Company, Philadelphia. 1947. Price, \$8.50.
- Jaundice: Its Pathogenesis and Differential Diagnosis.* By ELI RODIN MOVITT, M.D., Acting Chief of Medicine, Veterans Administration Hospital, Oakland, California, etc. 261 pages; 24 × 16 cm. Oxford University Press, New York. 1947. Price, \$6.50.
- Neutron Effects on Animals.* By THE STAFF OF THE BIOCHEMICAL RESEARCH FOUNDATION, DR. ELLICE McDONALD, Director, Newark, Delaware. 198 pages; 23.5 × 16 cm. The Williams & Wilkins Company, Baltimore. 1947. Price, \$3.00.
- A Primer of Cardiology.* By GEORGE E. BURCH, M.D., F.A.C.P., Associate Professor of Medicine, Tulane University School of Medicine, etc., and PAUL REASER, M.D., Instructor in Medicine, Tulane University School of Medicine, etc. 272 pages; 24 × 15.5 cm. Lea & Febiger, Philadelphia. 1947. Price, \$4.50.
- Procedure in Examination of the Lungs, with Especial Reference to the Diagnosis of Tuberculosis.* 3rd Ed. By ARTHUR F. KRAETZER, M.D., Associate Attending Physician, Lenox Hill Hospital, etc. Revised and with a Preface by JACOB SEGAL, M.D., F.A.C.P., F.C.C.P., Medical Director, Los Angeles Sanatorium, etc. 150 pages; 21 × 14 cm. The Oxford University Press, New York. Price, \$3.50.
- Recent Advances in Medicine: Clinical; Laboratory; Therapeutic.* 12th Ed. By G. E. BEAUMONT, M.A., D.M. (Oxon.), F.R.C.P., D.P.H. (Lond.), Physician to the Middlesex Hospital, etc., and E. D. DODDS, M.V.O., D.Sc., Ph.D., M.D., F.R.C.P., F.R.I.C., F.R.S. (Edin.), Courtauld Professor of Biochemistry in the University of London, etc. 422 pages; 21 × 13.5 cm. The Blakiston Company, Philadelphia. 1947. Price, \$6.00.
- Surgical Disorders of the Chest: Diagnosis and Treatment.* 2nd Ed. By J. K. DONALDSON, B.S., M.D., F.A.C.S. (Lt. Col., A.U.S.), Diplomate American Board of Surgery; etc. 485 pages; 24 × 16 cm. Lea & Febiger, Philadelphia. 1947. Price, \$8.50.

Ulcer: The Primary Cause of Gastric and Duodenal Ulcer—Diagnosis, Medical and Surgical Treatment, Prevention. By DONALD COOK, B.A., M.D., Chicago. 187 pages; 22.5 × 14 cm. Medical Center Foundation and Fund, Chicago. 1946. Price, \$5.00.

Unipolar Lead Electrocardiography: Including Standard Leads, Unipolar Extremity Leads and Multiple Unipolar Precordial Leads. By EMANUEL GOLDBERGER, B.S., M.D., Adjunct Physician, Montefiore Hospital, New York, etc. 182 pages; 24.5 × 16 cm. Lea & Febiger, Philadelphia. 1947. Price, \$4.00.

COLLEGE NEWS NOTES

A.C.P. POSTGRADUATE COURSES

During 1947 more than 1,000 physicians, the great majority of them Fellows and Associates of the College, were registered in one or more courses.

The quality of the College courses has been constantly improved through continued experience. A great host of the registrants feel that the conduct of these courses constitutes the most important activity of the College and it is almost the universal opinion, expressed by the registrants, that these courses are the finest available in America. The Dean of a prominent medical school recently said that the College postgraduate program would be one that any medical school would be very proud to foster.

The registration in the Autumn, 1947, was as follows:

No.	Title	Institution	Director	Registration
1	Internal Medicine	University of Pittsburgh School of Medicine	R. R. Snowden	20
3	Mechanics of Disease	Peter Bent Brigham Hospital, Boston	George W. Thorn	26
4	Hematology—Blood Disorders	Boston Institutions	William B. Castle	48
5	Physiological Basis for Internal Medicine	University of Pennsylvania Graduate School of Medicine, Philadelphia	Julius H. Comroe, Jr.	189
6	Advanced Cardiology	Southwestern Medical College, Dallas	Tinsley R. Harrison	38
8	Internal Medicine	University of Wisconsin Medical School, Madison	William S. Middleton	27
9	Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease	Massachusetts General Hospital, Boston	Paul D. White	89
10	Gastro-enterology	Graduate Hospital of the University of Pennsylvania, Philadelphia	Henry L. Bockus	41
11	Cardiovascular Disease	Yale University School of Medicine, New Haven	H. M. Marvin	28

Courses No. 2, Psychosomatic Medicine, at the University of Colorado School of Medicine, Denver; No. 7, Chemotherapy—New Drugs, at Boston University School of Medicine; and No. 12, General Medicine, at the University of Texas School of Medicine, Galveston, were cancelled.

Spring, 1948 Schedule of Courses

No. 1, MEDICAL ASPECTS OF RADIOACTIVE SUBSTANCES—Naval Medical Center, Bethesda, Md.; February 17–27. (First week devoted to nuclear physics, and optional; physicians may register only for second week, February 23–27, if desired.)

- No. 2, PHYSICAL MEDICINE—Mayo Clinic, Rochester, Minn.; Director, Frank H. Krusen, M.D., F.A.C.P.; March 22-27.
- No. 3, CARDIOLOGY—University of Southern California. School of Medicine, Los Angeles; Director, George C. Griffith, M.D., F.A.C.P.; April 12-17.
- No. 4, ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION—Massachusetts General Hospital, Boston; Director, Conger Williams, M.D.; May 10-15.
- No. 5, INTERNAL MEDICINE—Gallinger Municipal Hospital, Washington, D. C.; Director, Wallace M. Yater, M.D., F.A.C.P.; May 17-22.
- No. 6, CLINICAL ALLERGY—Roosevelt Hospital, New York City; Director, Robert A. Cooke, M.D., F.A.C.P.; May 17-29.
- No. 7, CLINICAL NEUROLOGY—Jefferson Medical College, Philadelphia; Director, Bernard J. Alpers, M.D., F.A.C.P.; May 24-29.
- No. 8, PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE—University of Illinois Medical School, Chicago; Director, A. C. Ivy, M.D., F.A.C.P.; May 31-June 5.
- No. 9, DIABETES AND METABOLIC DISEASES—New England Deaconess Hospital, Boston; Director, Elliott P. Joslin, M.D., F.A.C.P.; July 12-16.

Fees for all courses, with the exception of No. 6, will be \$30.00 per week to A.C.P. members, and \$60.00 to non-members. No fee will be charged to medical officers in the Army or Navy in the case of Course No. 1. The fee for Course No. 6, which is purely a clinical course limited to eight physicians, will be \$60.00 per week to A.C.P. members, and \$120.00 to non-members.

Course No. 3 is specifically organized as a pre-Convention course at Los Angeles during the week just preceding the 29th Annual Session of the College at San Francisco, April 19-23, and will afford an opportunity to members to take this course on the West Coast just before attending the Annual Meeting of the College.

Detailed Bulletins of each course will be published in early January and distributed to all members of the College and to non-members requesting copies. Inquiries should be addressed to the Executive Secretary, The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

AMERICAN COLLEGE OF PHYSICIANS RESEARCH FELLOWSHIPS IN MEDICINE 1948 AWARDS

The Board of Regents of the College, on nomination of the Committee on Fellowships and Awards, awarded six Research Fellowships in Medicine for the year beginning July, 1948, at their meetings in Philadelphia on November 22 and 23, 1947. The awards were made to the following physicians.

CHARLES GORDON CAMPBELL, M.D., C.M., Vancouver, B. C., Can. Dr. Campbell attended the University of British Columbia and is a graduate of the McGill University Faculty of Medicine, 1945. He interned in the Royal Victoria Hospital, Montreal, 1945-46, and has held appointments in the Vancouver General Hospital as Assistant Resident in Medicine, 1946-47, and as Fellow in Cardiology, 1947-48. Dr. Campbell will undertake studies of the basic physiology of certain cardiovascular problems in the Department of Physiology of McGill University, under the supervision of Professor Hebbel E. Hoff.

FRANK HERBERT GARDNER, M.D., San Bernardino, Calif. Dr. Gardner attended Northwestern University (B.S., 1941; M.D., 1944). He served as intern and Assistant Resident in the San Francisco Hospital, 1944-46, and as Senior Assistant Resident in the University of California Hospital, 1946-47. Presently Fellow in Medicine in the Boston City Hospital, Dr. Gardner will conduct studies in the Thorndike Memorial Laboratory under the direction of William B. Castle, M.D., F.A.C.P., and Thomas H. Ham, M.D., F.A.C.P., of the mechanism and clinical application of the osmotic fragility test.

SAMUEL P. MARTIN, M.D., Durham, N. C. Dr. Martin's premedical and medical courses were taken at Washington University, St. Louis, where he received the M.D. degree in 1941. He interned in the Barnes Hospital, St. Louis, 1942-43, and served there also as Assistant Resident in Medicine, 1943-44. Dr. Martin served in the Army from 1944 until 1947. He is presently Resident in Medicine in the Duke University Hospital. With the aid of the Fellowship, Dr. Martin will undertake studies of bacterial metabolism in the Rockefeller Institute for Medical Research, New York, N. Y., under the direction of Dr. René J. Dubos.

PERITZ SCHEINBERG, M.D., Miami, Fla. Now Assistant Resident in Medicine in the Duke University Hospital, Dr. Scheinberg attended Emory University, where he received the A.B. degree in 1941, and the M.D. degree in 1944. He subsequently served as intern and Assistant Resident in Medicine in the Grady Memorial Hospital, Atlanta, Ga. Dr. Scheinberg served in the U. S. Naval Reserve, 1945-46. He will conduct an investigation of cerebral circulation and peripheral vascular flow in normal and hypertensive persons in the Duke University Hospital under the direction of Eugene A. Stead, Jr., M.D., F.A.C.P.

LUTFU LAHUT UZMAN, M.D., Istanbul, Turkey. Dr. Uzman will conduct studies, now under way, with Dr. J. Folch-Pi, in the Department of Scientific Research of the McLean Hospital, Waverley, Mass., on the isolation and characterization of brain proteins and their rôle in health, disease and senescence. Dr. Uzman received the B.S. degree from the University of Istanbul Faculty of Science in 1940. Following several years of study in the Medical School of that institution, he transferred to the Harvard Medical School and completed his work for the M.D. degree there in 1946. He interned in the Boston City Hospital, Neurology Service, 1946-47, and has since held appointment as Assistant in the McLean Hospital.

JOHN MARTIN WELLER, M.D., Ann Arbor, Mich. Dr. Weller completed his undergraduate studies at the University of Michigan in 1940 and received the M.D. degree from Harvard Medical School in 1943. He served as Medical House Officer, Peter Bent Brigham Hospital, Boston, from January to October, 1944; as Assistant Resident in Medicine in the Vanderbilt University Hospital, Nashville, Tenn., from October, 1944, to July, 1945. Since January of 1946, Dr. Weller has been Medical Resident in the Veterans Administration Hospital, Hines, Ill. Dr. Weller's appointment to the first Alfred Stengel Research Fellowship of the American College of Physicians will enable him to undertake, with Professor A. Baird Hastings in the Department of Biologic Chemistry of Harvard Medical School, studies concerning the ionic patterns of the intracellular fluids and their influence on enzymatic reactions; of acid-base balance in tissues other than skeletal muscle tissue.

The American College of Physicians takes pleasure in announcing that on December 3, 1947, Frank McLeod Wiseley, M.D., F.A.C.P., Findlay, Ohio, became a Life Member.

The Fourth Annual Clinical Conference of the Chicago Medical Society will be held at the Palmer House, Chicago, March 2-5, 1948. The Conference will consist of lectures, panel and round-table discussions, and clinico-pathologic seminars. Scientific and technical exhibits will be a feature of the meeting. Physicians, whether general practitioners or specialists, are invited to attend the Conference. Hotel reservations may be made directly with the Palmer House.

SPECIALTY BOARD EXAMINATIONS

American Board of Dermatology and Syphilology, Inc., 66 E. 66th St., New York 21, N. Y.; George M. Lewis, M.D., Secretary-Treasurer. Oral examinations

for Group A and B candidates will be held in Philadelphia, April 2-4, 1948. Written examinations for Group B will be given on February 16, 1948, in various cities in the United States.

At the meeting of the Board in Chicago, October 24-26, 1947, there were 81 candidates, of whom 55 were successful. There are now 924 certified diplomates on the roster of the American Board of Dermatology and Syphilology, Inc.

American Board of Internal medicine, 1 W. Main St., Madison 3, Wis.; William A. Werrell, M.D., Assistant Secretary-Treasurer. Oral examinations will be conducted at San Francisco in April, 1948, and in Chicago in June, 1948, both periods immediately preceding the Annual Session and Convention of the American College of Physicians and the American Medical Association, respectively. The closing date for registration for oral examinations is February 1, 1948.

The Board's next written examination will be on October 18, 1948, with a closing date for registration of June 1, 1948.

The American Board of Pediatrics, Inc., 718 Royal Union Bldg., Des Moines, Iowa; Lee F. Hill, M.D., Secretary-Treasurer. The next written examinations will take place on March 12, 1948. Oral examinations are scheduled for April 23-25, 1948, in Cleveland, Ohio; and for June 25-27, 1948, in Chicago, Ill.

The American Board of Physical Medicine, 30 N. Michigan Ave., Chicago 2, Ill.; Robert L. Bennett, M.D., Secretary-Treasurer. The next examination period will be two days prior to the Annual Convention of the American Medical Association, June, 1948, Chicago, Ill.

The Lois Grunow Memorial Clinic, Phoenix, Ariz., will present an instructional program February 19-21, 1948. The following will be among the contributors to the program. Francis D. Murphy, M.D., F.A.C.P., Professor and Head of the Department of Medicine, Marquette University; Lester W. Paul, M.D., F.A.C.R., Professor of Radiology, University of Wisconsin Medical School; Frank H. Lahey, M.D., F.A.C.S., Lahey Clinic, Boston, Mass.; Vincent J. O'Connor, M.D., F.A.C.S., Professor and Chairman of Department of Urology, Northwestern University Medical School; Elvira Goettsch, M.D., Assistant Professor of Pediatrics, University of Southern California; William H. Bickel, M.D., F.A.C.S., Section on Orthopedics, Mayo Clinic, Rochester, Minn.; and the following members of the Clinic staff: Henry G. Williams, M.D., F.A.C.S., Department of Surgery; Hugh Wilson, M.D., Department of Clinical Laboratory; Norton J. Wood, D.D.S., Department of Orthodontia; John Eisenbeiss, M.D., Department of Neurosurgery; O. W. Thoeny, M.D., F.A.C.S., Department of Eye, Ear, Nose and Throat.

IMPORTANT CONTRIBUTION TO COLLEGE LIBRARY

H. Sheridan Baketel, A.M., M.D., F.A.C.P., Director of the Reed & Carnick Institute for Medical Research, Jersey City, N. J., has presented to the College Library on behalf of the Institute the two volume *Opera Omnia* of Vesalius, the famous Boerhaave and Albini collection. This edition was published in Leyden in 1725 and contains plates and many engravings by Jan Wandelaar. This rare example of a medical classic has been described as follows:

First Collected Edition, a magnificent publication issued in commemoration of the 200th anniversary of the birth of Vesalius. The woodcuts of the *Fabrica* and of the *Epitome* are very beautifully copied and engraved on copper in the original size by Jan Wandelaar. The title-page is engraved after the edition of 1543. Oporinus' monogram, however, is omitted and the architecture slightly changed. The remaining wood engravings are copied entirely, with the additions, from the edition of 1555.

All the woodcuts of the *Epitome* are re-engraved, without exception. Vesalius' *Epistola docens venan axillarem*, etc., is omitted, also the Vesalian plates of 1538; on the other hand it contains *De radice Chynae*, Gabr. Fallopii *observationes anatomicae* (against Vesalius) and Vesalii *anatomicarum G. Fallopii anatomicae examen* (a rejoinder), and the posthumous *Chirurgia magna* in Vesalius' own handwriting which contains a number of small illustrations.—Fine, uncut copy; lacks plates 3, 74 and 75.—With the Edward C. Streeter bookplate.

THE EASTERN PENNSYLVANIA REGIONAL MEETING

The annual Eastern Pennsylvania Regional Meeting was held at the Warwick Hotel, Philadelphia, on November 21, 1947, under the Chairmanship of Dr. E. L. Bortz, College Governor for Eastern Pennsylvania. In addition to the Eastern Pennsylvanians, members from near-by New Jersey and Delaware were invited. In addition to an excellent scientific program, a reception and dinner were held in the evening at which the Officers and Regents of the College were in attendance as well as the deans of the various medical schools in Philadelphia, the President of the College of Physicians of Philadelphia, and of the Philadelphia County Medical Society. The attendance was gratifying, there being a total of 267 officially registered, of whom 193 were members of the College and 74 were guests.

Fellows and Associates of the American College of Physicians in South Carolina who were in attendance at the Post-Graduate Seminar of the Medical College of South Carolina, November 6, 1947, joined for a luncheon. College affairs were discussed at the luncheon, which was well attended.

The Omaha Mid-West Clinical Session, of which J. D. McCarthy, M.D., F.A.C.P., Omaha, College Governor for Nebraska, is a member of the Executive Committee, held its 1947 Session October 27-31. The meeting was a very successful one with a registration of 1,185. The program included as participants the following members of the College: F. Lowell Dunn, M.D., F.A.C.P., John F. Gardiner, M.D., F.A.C.P., Ernest Kelley, M.D., F.A.C.P., John R. Kleyla, M.D., F.A.C.P., Harold C. Lueth, M.D., F.A.C.P., Ernest L. MacQuiddy, M.D., F.A.C.P., Warren Thompson, M.D., F.A.C.P., Raymond L. Traynor, M.D., F.A.C.P., and J. Harry Murphy (Associate), all of Omaha. Guest speakers included Nelson W. Barker, M.D., F.A.C.P., Rochester, Minn.; Edward L. Bortz, M.D., F.A.C.P., Philadelphia; Franklin G. Ebaugh, M.D., F.A.C.P., Denver; Victor Johnson, M.D., F.A.C.P., Rochester, Minn.; Donald McCarthy, M.D., F.A.C.P., St. Paul; and Walter L. Palmer, M.D., F.A.C.P., Chicago.

Charles E. Kossmann, M.D., F.A.C.P., New York, N. Y., formerly Lieutenant Colonel, A.U.S., has been awarded the Legion of Merit for his accomplishment in the production of the "Flight Surgeon's Handbook," while Chief of the Department of Aviation Medicine of the Army Air Forces School of Aviation Medicine.

R. R. Snowden, M.D., F.A.C.P., College Governor for Western Pennsylvania, has been awarded the honorary degree of Doctor of Science by Washington and Jefferson College, Washington, Pa., at exercises held on November 1, 1947.

Oscar B. Hunter, M.D., F.A.C.P., Washington, D. C., has been elected to the position of President-Elect of the Southern Medical Association.

Alphonse McMahon, M.D., F.A.C.P., St. Louis, Mo., was elected to the position of President-Elect of the Mississippi Valley Medical Society at the November meeting of the Society's Board of Directors. Harold Swanberg, M.D., F.A.C.P., and Ralph McReynolds, M.D., F.A.C.P., both of Quincy, Ill., were elected Secretary-Treasurer and Account Officer. The next annual meeting of the Society will take place at Springfield, Ill., September 29-October 1, 1948, under the Presidency of Willard O. Thompson, M.D., F.A.C.P., Chicago, Ill.

To receive consideration for the 1948 annual essay prize of the Mississippi Valley Medical Society, essays must be submitted not later than May 1, 1948, to the Secretary of the Society. The prize of \$100.00, a gold medal and a certificate of award is offered for the best unpublished essay on any subject of general medical interest and of practical value to the general practitioner of medicine.

The Fifty-eighth Annual Convention of the Association of the American Medical Colleges was held recently at Sun Valley, Idaho. Among the newly elected officers, Walter A. Bloedorn, M.D., F.A.C.P., Washington, D. C., was elected President; J. Roscoe Miller, M.D., F.A.C.P., Chicago, Ill., President-Elect; and Ward Darley, Jr., M.D., F.A.C.P., Denver, Colo., Member of the Executive Council.

George B. Dowling, M.D., F.A.C.P., Washington, formerly Captain in the U. S. Navy, has recently been appointed Deputy Administrator in the American Red Cross to assist Ross T. McIntire, M.D., F.A.C.P., who is directing that organization's program for the procurement and distribution of whole blood.

Andrew C. Ivy, M.D., Ph.D., F.A.C.P., Chicago, Vice President of the University of Illinois, delivered the Convocation address before the American College of Surgeons at New York City, September 12, 1947, on "Liberal Medical Education."

AMERICAN COLLEGE OF SURGEONS PRESENTS LECTURE TABLE AND LECTERN TO THE ROYAL COLLEGE OF SURGEONS OF ENGLAND

On September 22, 1947, at Lincoln's Inn Fields, London, the American College of Surgeons formally presented to the Royal College of Surgeons of England a beautifully designed lecture table and a lectern "as a token of mutual friendship." At the same exercises, Honorary Fellowships were conferred by the Royal College of Surgeons of England on the following Officers and Regents of the American College of Surgeons: Arthur Wilburn Allen, Boston, President; Irvin Abell, Louisville, Chairman of the Board of Regents; Frank Howard Lahey, Boston, former President; Dallas Burton Phemister, Chicago, President Elect; Alfred Blalock, Baltimore, Regent. William Edward Gallie, Toronto, former President, was honored with the Honorary Gold Medal of the Royal College of Surgeons of England, "the most exclusive emblem of merit of the Royal College."

Evarts Ambrose Graham, St. Louis, former President of the American College of Surgeons, received from the Royal College the rare award of the Lister Medal.

The Honorary Medal of the Royal College of Surgeons of England was instituted in 1802. The leading considerations in awarding this medal are liberal acts or distinguished labors, researches, and discoveries, eminently conducive to the improvement of natural knowledge and of the healing art.

The Lister Award consists of a sum of £500, together with a bronze medal, awarded every three years, in recognition of distinguished contributions to surgical science, the recipient, who may be of any nationality, being required to give an address in London under the auspices of the Royal College of Surgeons.

The American Pharmaceutical Manufacturers' Association presented its distinguished award for 1947 to the American Medical Association at a meeting in New York on December 16. The award is made on nomination by a Scientific Advisory Committee which includes among its members David P. Barr, M.D., F.A.C.P., New York, Past President of the College; Anton J. Carlson, M.D., M.A.C.P., Chicago, Ill.; H. C. Hinshaw, M.D., F.A.C.P., Rochester, Minn.; Chester S. Keefer, M.D., F.A.C.P., Boston; John B. Youmans, M.D., F.A.C.P., Chicago. The award recognizes fundamental contributions in medical science to the public health as well as progress in basic research in drug therapy. The award was presented by Dr. Perrin H. Long of Baltimore in behalf of the A.P.M.A. and was accepted for the American Medical Association by its President-Elect, Roscoe L. Sensenich, M.D., F.A.C.P., South Bend, Ind.

Dr. Walter O. Klingman, F.A.C.P., recently accepted an appointment as Associate Professor of Neuropsychiatry in the University of Virginia's School of Medicine. He was formerly connected with the Neurological Institute of New York.

Charles E. Lyght, M.D., F.A.C.P., who has been Director of Health Education with the National Tuberculosis Association of New York City for the past five years, joined the staff of the Medical Division of Merck & Co., Inc., Rahway, N. J., December 1, 1947.

ELECTIONS TO MEMBERSHIP—THE AMERICAN COLLEGE OF PHYSICIANS

Philadelphia, Pa., November 23, 1947

(Lower case indicates Associates; FULL CAPITALS INDICATE FELLOWS)

Abel, Oliver, Jr., St. Louis, Mo.

ABERNETHY, THEODORE JUDSON, Washington, D. C.

Ailts, Bernard Henry, Wood, Wis. (V.A.)

ALPERS, BERNARD JACOB, Philadelphia, Pa.

AMTMAN, LEO, Chicago, Ill.

Angell, Rudolph, Rochester, N. Y.

Arbuse, David Irving, New York, N. Y.

ARNDAL, OTTO, Glendale, Calif.

Atlas, Donald Herman, Evanston, Ill.

BABEY, ANDREW MICHAEL, Brooklyn, N. Y.

BARRIER, CHARLES WESLEY, Ft. Worth, Tex.

BARTHOLOMEW, RAYMOND KENNETH, Dayton, Ohio

BEARD, EDMUND EARL, Cleveland, Ohio

BECK, DAVID, New York, N. Y.

Berger, Herbert, Staten Island, N. Y.

BLAIN, DANIEL, Washington, D. C. (V.A.)

Blalock, Tully Talbot, Atlanta, Ga.

BLISS, RAYMOND WHITCOMB, (MC), USA
 Boyer, Paul Kenneth, Summit, N. J.
 Brandt, Charles Richard, Mechanicsburg, Pa.
 Braunstein, John Rutley, Cincinnati, Ohio
 Breuhaus, Herbert Charles, Chicago, Ill.
 Brookens, Norris L., Urbana, Ill.
 Brussel, James Arnold, Willard, N. Y.
 Bucholz, Donald John, Omaha, Nebr.
 BURNEY, LEROY EDGAR, Indianapolis, Ind.

Calvy, George Lloyd, (MC), USN
 Cammerer, Herbert Richard, Dayton, Ohio
 CARDON, LEONARD, Chicago, Ill.
 Carroll, Francis Brian, Waban, Mass.
 Charr, Robert, Philadelphia, Pa.
 Chester, Edward Milton, Berea, Ohio
 Clark, Arthur Paul Carman, Calgary, Alta, Can.
 Cochran, William Lloyd, Ann Arbor, Mich.
 Cohen, Stanley, New Orleans, La.
 Cole, Seymour Lewy, Los Angeles, Calif.
 Coleman, Francis Carter, Des Moines, Iowa
 CONNOLLY, ALOYSIUS JOHN BERCHMANS, Washington, D. C.
 COOMBS, FREDERICK STANLEY, JR., Youngstown, Ohio
 Cooper, Talbert, Rochester, Minn.
 Correll, Howard Leroy, Milwaukee, Wis.
 Cosby, Richard Sheridan, Pasadena, Calif.
 CRAMER, CHARLES, Jackson Heights, N. Y.
 Crampton, Joseph Hamilton, Seattle, Wash.
 Creel, Wylie Fackler, Austin, Tex.
 Curtis, Harold Goldsmith, Cleveland, Ohio
 Curtis, Raleigh Robert, Temple, Tex.
 Cutter, Edward Parker, Clarksville, Tenn.

Dale, Mark, Detroit, Mich.
 DANIELS, EINAR ROBERT, Milwaukee, Wis.
 Danstrom, John Richard, Oklahoma City, Okla.
 DARNALL, CHARLES MILTON, Austin, Tex.
 Davis, C(lare) Nelson, Philadelphia, Pa.
 Dear, Richard Hamilton Bryarlie, (MC), USA
 DeFEO, HERMAN FELIX, Chicago, Ill.
 Del Vecchio, James John, Wheeling, W. Va.
 Denman, William Emmett, Jr., Memphis, Tenn.
 Dennison, Alfred Dudley, Jr., Maplewood, N. J.
 Doerner, Alexander Andrew, USPHS
 DOLKART, RALPH ELSON, Chicago, Ill.
 Dumanis, Abraham Aaron, Flushing, N. Y.
 Dunbar, William, Philadelphia, Pa.

Eagan, John Charles, Los Angeles, Calif.
 Erdmann, Albert John, Jr., New York, N. Y.
 ERICKSON, ELDON WESLEY, Detroit, Mich.
 Erwin, Herbert Jones, St. Louis, Mo.

FAHR, GEORGE EDMESTON, Minneapolis, Minn.
 Fanson, Anna Ethel, Pasadena, Calif.
 FARQUHARSON, RAY FLETCHER, Toronto, Ont., Can.
 Feder, Aaron, Jackson Heights, N. Y.
 FINKELSTEIN, DAVID, Philadelphia, Pa.
 Flance, Israel Jerome, St. Louis, Mo.
 Flannery, Wilbur Eugene, New Castle, Pa.
 Fleming, J(acob) Will(iam), Jr., Moberly, Mo.
 FLEMING, RALPH GIBSON, Durham, N. C.
 Friedland, Carl Kampton, Philadelphia, Pa.
 FRIST, THOMAS FEARN, Nashville, Tenn.
 FULGHUM, CHARLES BENNETT, SR., Milledgeville, Ga.
 Fusting, William Hammond, Baltimore, Md.

Gambill, William Dudley, Indianapolis, Ind.
 Garvin, Robert Odell, Pittsburgh, Pa.
 GELBACH, PHILIP DELMONT, Detroit, Mich.
 Gemmell, John Patmore, Winnipeg, Man., Can.
 GILMOUR, MONROE TAYLOR, Charlotte, N. C.
 Golding, Frank Cunningham, El Paso, Tex.
 GOMPERTZ, JOHN LANGDON, Oakland, Calif.
 Goodman, Joseph Irving, Shaker Heights, Ohio
 Gootnick, Abraham, Memphis, Tenn. (V.A.)
 GOULEY, BENJAMIN ALEXIS, Philadelphia, Pa.
 GREEN, MAYER ALBERT, Pittsburgh, Pa.
 Greenfield, Herbert, Newark, N. J.
 Greenwald, Louis, New York, N. Y.
 Grishman, Arthur, New York, N. Y.

Harris, Richard Lamar, Los Angeles, Calif. (V.A.)
 Harrison, Francis French, Cooperstown, N. Y.
 HARTWELL, ALFRED STEDMAN, Honolulu, T. H.
 HASSETT, F(LORENCE) SULLIVAN, Elmira, N. Y.
 Hatton, Don Virgil, Huntington, W. Va.
 Hauenstein, Virgil Dee, Cincinnati, Ohio
 Hause, Welland Angel, (MC), USA
 Hay, William Edwin, Denver, Colo.
 HAYES, PAUL, (MC), USA
 HEDGES, ROBERT NATHANIEL, Chicago, Ill.
 Henderson, Allison Burney, Detroit, Mich.
 Henry, J(ennings) Lamont, Atlanta, Ga.
 HERNDON, JAMES HENRY, Dallas, Tex.
 Herzog, Robert Simon, Chicago, Ill.
 HILDEBRAND, ALICE GRACE, Seattle, Wash.
 Hiles, Charles Hall, Wheeling, W. Va.
 Hill, Alfred Humphrey, San Antonio, Tex.
 Hock, Charles William, Augusta, Ga.
 HOFFMAN, BYRON JAY, Atlanta, Ga.
 Holley, Howard Lamar, Birmingham, Ala.
 Holmes, Joseph Henry, Denver, Colo.
 Hortenstine, John Campbell, Winchester, Va.
 Howell, Thomas Wellington, Newark, N. J.
 Hubbs, Roy Sears, Palo Alto, Calif. (V.A.)
 HUMPHREY, ARTHUR ALLAN, Battle Creek, Mich.

ISRAEL, HAROLD LOUIS, Philadelphia, Pa.
Izenstein, Louis Arthur, Springfield, Mass.

Jarrett, Thirl Edwin, (MC), USN
Jarvis, James Armstead, Kansas City, Mo.
Jastremski, Bruno, (MC), USA
Johnson, Chester Earle, Jr., Tuscaloosa, Ala.
Johnson, John Beauregard, Washington, D. C.
JOHNSON, SCOTT, New York, N. Y.
JONES, EDGAR, Nashville, Tenn.

KAPLAN, BERNARD IRVING, Ossining, N. Y.
Karl, Michael Meyer, St. Louis, Mo.
Kemble, Edward Ernest, Erie, Pa.
Kimball, Stanley, Dedham, Mass.
Kindschi, Leslie George, Monroe, Wis.
Kirshen, Martin Moses, Chicago, Ill.
KIRSNER, JOSEPH BARNETT, Chicago, Ill.
KIPSTEIN, MELVIN BYRON, St. Louis, Mo.
KLOSK, EMANUEL, Newark, N. J.
KOSSMANN, CHARLES EDWARD, New York, N. Y.
Krinsky, Charles Morris, New London, Conn.
Kutzer, Max, Syracuse, N. Y.

Lamberta, Frank, Jamaica, N. Y.
Lang, Valorus Frederick, Milwaukee, Wis.
Latimer, John Wilmer, Jr., Washington, D. C.
Lawler, Edmund Griffin, Chicago, Ill.
LEAVELL, BYRD STUART, Charlottesville, Va.
Levy, Harold, Brooklyn, N. Y.
Levy, Louis, II, New Orleans, La.
Levy, Marvin Shephard, Beverly Hills, Calif.
Lieberson, Abraham, New York, N. Y.
LINN, GEORGE CHARLES, New York, N. Y.
Lipsitz, Morton Hirsch, Buffalo, N. Y.
LIPTON, HARRY ROBERT, Atlanta, Ga.
LITTERAL, EMMETT BRYAN, (MC), USA
LITWINS, JOSEPH, New York, N. Y.
LUCIA, SALVATORE PABLO, San Francisco, Calif.

Maimon, Samuel Newman, Dayton, Ohio
Mansfield, James Scott, Boston, Mass.
Manulis, Fred(erick) Everett, Palm Beach, Fla.
Marshall, Frank Anton, Weehawken, N. J.
Mason, Eugene Edgar, Dallas, Tex.
McCaffrey, Maurice Henry, Pittsburgh, Pa.
McCollum, Wiley Thomas, Oklahoma City, Okla.
McConahay, Harold Arthur, Holdrege, Nebr.
MENEFEE, ELIJAH EUGENE, JR., Durham, N. C.
MERKLE, CLARENCE EDWARD, Alton, Ill.
Merrick, Benjamin August, Dallas, Tex.
MINISH, LAWRENCE T., JR., Louisville, Ky.
MIRSKY, I(SADORE) ARTHUR, Cincinnati, Ohio
MITCHELL, ROBERT HARTWELL, Ft. Worth, Tex.

Moe, Allan Eugene, Fargo, N. D.
MOENCH, LOUIS GARDNER, Salt Lake City, Utah
MOLONEY, WILLIAM CURRY, Boston, Mass.
MONACO, THOMAS CLIFFORD, Jamaica, N. Y.
MONTOM, RAYMOND WALTER, Detroit, Mich.
Morgan, Allan Vincent, Pittsburgh, Pa.
Moseley, Vince, Charleston, S. C.
Murphy, Albert Vincent, Omaha, Nebr.

Naide, Meyer, Philadelphia, Pa.
Nevin, Robert John, Washington, Pa.
Nichols, Ralph Gibbs, Knoxville, Tenn.
NORMAN, JAMES KINDRED, Ft. Worth, Tex.
Notier, Victor Anthony, Grand Rapids, Mich.
Numainville, Leon Joseph (MC), USA
Nyiri, William, Newark, N. J.

OCHS, LOUIS, JR., New Orleans, La.
OHLER, W(ILLIAM) RICHARD, Jamaica Plain, Mass.
Oxman, Albert Charles, Denver, Colo.
Ozarin, Lucy Deborah, Buffalo, N. Y. (V.A.)

PACKARD, EDWARD NEWMAN, Trudeau, N. Y.
Parker, Ralph Chandler, Jr., (MC), USN
Partch, Wallace Taylor, Oakland, Calif.
PAULL, ROSS, La Jolla, Calif.
PELLICANO, VICTOR LOUIS, Niagara Falls, N. Y.
PERRY, T(HORNTON) TAYLOE, III, Washington, D. C.
Petersen, Drew Mathew, Ogden, Utah
PFEIFFER, MILDRED CLARA JULIA, Merion Station, Pa.
Plessinger, Virgil Allen, Cincinnati, Ohio
PORTER, RENO RUSSELL, Richmond, Va.
Post, John, Chicago, Ill.
PRIDDLE, WILLIAM WELMORE, Toronto, Ont., Can.
Proudfit, William Lyle, Cleveland, Ohio

Radke, Ryle August, (MC), USA
Rafferty, Theodore Newell, New Orleans, La. (V.A.)
Rand, Harold, Miami, Fla.
RANGES, HILMERT ALBERT, New Rochelle, N. Y.
Rappaport, Henry, Washington, D. C. (V.A.)
RAY, EDWARD SCOTT, Richmond, Va.
REDISH, JULES, Lynbrook, N. Y.
REIN, GERALD NORMAN, Benton Harbor, Mich.
Rieber, Charles Wolfe, Forest Hills, N. Y.
Rifkin, Harold, New York, N. Y.
ROBERTS, JOSEPH THOMAS, Washington, D. C.
Rosenblatt, William, Wichita Falls, Tex.
Rosenthal, Sydney, Newark, N. J.
Ross, John Richard, Milton, Mass.
Rudnikoff, Isadore, Yonkers, N. Y.
Rumball, John Marcus, Coral Gables, Fla. (V.A.)
Ryan, Raymond Charles, Jamaica, N. Y.

Sackey, Maurice Seville, Philadelphia, Pa.
 SAUER, WILLIAM GEORGE, Rochester, Minn.
 Scanlan, William Dennis, Jr., Brooklyn, N. Y.
 SCHEIFLEY, CHARLES HOLLAND, Rochester, Minn.
 SCHERLIS, SIDNEY, Baltimore, Md.
 Schlachman, Milton, Corona, N. Y.
 SCHNEIERSON, S(OL) STANLEY, New York, N. Y.
 SCHUCK, CARL ALFRED, Hamilton, Ohio
 SCHWEMLEIN, GEORGE XANTHIAN, Cincinnati, Ohio
 Sears, William Norman, Palo Alto, Calif.
 SEYBOLD, EDWARD GEORGE, Toledo, Ohio
 Shafer, Harold Camden, Bay City, Mich.
 Shafer, June Carol, New York, N. Y.
 SHAY, HARRY, Philadelphia, Pa.
 Shechter, Fred Ralph, Philadelphia, Pa.
 SHILLITO, FREDERICK HOPKINS, New York, N. Y.
 Siglin, Irvin Sidney, Chicago, Ill.
 Silver, Aaron, New York, N. Y.
 Simkins, Samuel, Philadelphia, Pa.
 Simmons, Eugene Earl, Omaha, Nebr.
 Skubi, Kazimer Bogar, Seattle, Wash.
 Sloan, Fred Ries, (MC), USA
 Smith, John Goodrich, Rocky Mount, N. C.
 Soderstrom, Kenneth Malcolm, Seattle, Wash.
 SOKOLOV, RAYMOND A., Detroit, Mich.
 Spencer, Gerald Arthur, New York, N. Y.
 STARRS, ROBERT ALPHONSUS, Ottawa, Ont., Can.
 Sterne, Eugene Herman, Jr., Cincinnati, Ohio
 Steward, Williams Dean, Orlando, Fla.
 STEWART, SLOAN GIFFIN, Atlantic City, N. J.
 Stine, Leonard Alvin, Chicago, Ill.
 Strauss, Victor, Cincinnati, Ohio
 Stroebel, Charles Frederick, Jr., Rochester, Minn.
 Stuckey, Charles LeGrand, Charlotte, N. C.
 Styron, Charles Woodrow, Raleigh, N. C.
 Sweet, Herbert Chittenden, Affton, Mo.
 SWEIGERT, CHARLES FRANCIS, San Francisco, Calif.

 Taubenhaus, Matthew, Chicago, Ill.
 TAYLOR, JAMES SHERWOOD, (MC), USA
 TAYLOR, LESTER, Cleveland, Ohio
 TAYLOR, ROBERT DEWEY, Cleveland, Ohio
 Thal, William S., Toledo, Ohio
 Thompson, George Newton, Los Angeles, Calif.
 Thompson, Joseph James, Gloversville, N. Y.
 Tierney, Gerald Miles, (MC), USA
 Tierney, Nicholas Archibald, Miami Beach, Fla.
 TOWNSEND, STUART ROSS, Montreal, Que., Can.
 Toy, Calvert Rogers, New Brunswick, N. J.
 Tredway, John Buffington, Erie, Pa.

UHR, NATHANIEL, Topeka, Kans. (V.A.)
 Underwood, Franklin Judson, Portland, Ore.

VOORHIES, NORTON WILLIAM, New Orleans, La.

Ward, George Joseph, Poughkeepsie, N. Y.

Warren, Irving Aaron, Detroit, Mich.

Wasserman, Louis Robert, New York, N. Y.

Watson, (Ruth) Janet, Brooklyn, N. Y.

Watts, Frederick Beemer, Grosse Pointe Woods, Mich.

Weaver, Myron McDonald, Minneapolis, Minn.

Webster, John Joseph, New York, N. Y.

Weeks, Kenneth Durham, Rocky Mount, N. C.

WENDKOS, MARTIN HOWARD, Philadelphia, Pa.

WHITE, BENJAMIN VROOM, Hartford, Conn.

Wilcox, Abbott Yates, Jr., Cincinnati, Ohio

Wilder, Russell Morse, Jr., Minneapolis, Minn.

Wilkerson, Hugh Lyon Clements, USPHS

WILLIAMS, ROBERT HARDIN, Newton Lower Falls, Mass.

Willis, James Garnett, Fredericksburg, Va.

WILNER, PAUL ROBERT, Washington, D. C.

Wilson, Keith Singleton, St. Louis, Mo.

WILSON, W(ALTER) HOWARD, Raleigh, N. C.

WINSOR, TRAVIS WALTER, Los Angeles, Calif.

Wise, Robert Allen, Temple, Tex. (V.A.)

WOLFRAM, DONALD J., Indianapolis, Ind.

Wolfson, Samuel Abraham, Los Angeles, Calif.

WOSIKA, PAUL HENRY, Chicago, Ill.

WRIGHT, ROBERT BROY, Baltimore, Md.

Young, Bascom Brockenbrough, Wingdale, N. Y.

Young, Dennison, New York, N. Y.

Young, John David, Jr., Memphis, Tenn.

Younge, Walter Archibald, St. Louis, Mo.

Youngman, Robert Armstrong, Lincoln, Nebr.

ZAVOD, WILLIAM ABRAHAM, Mount Vernon, N. Y.

Zieman, Alphonse Hays, Mobile, Ala.



ERNEST BRENNAN BRADLEY

OBITUARY

DR. ERNEST BRENNAN BRADLEY

Ernest Brennan Bradley, A.B., M.D., M.A.C.P., Lexington, Ky., died November 12, 1947, after a long illness from an extensive encephalopathy associated with several circulatory episodes, involving the brain and heart.

Dr. Bradley was born May 16, 1877, at Lexington, Ky. He received his A.B. degree from Transylvania College in 1895; his medical degree from the University of Michigan Medical School in 1904. Interned at the New York City Hospital, Welfare Island; City Bacteriologist, Lexington, 1908-25; Health Officer, Fayette County, 1909-24; Chairman, Fayette County Board of Health, 1924-38; Member, Lexington City Board of Health, 1932-38; Chairman, combined Fayette County and Lexington City Board of Health, 1938—; Member, the Lexington Clinic, 1920—; Visiting Physician, St. Joseph's Hospital (since 1907) and Good Samaritan Hospital (since 1909); Member, Medical Advisory Board, Julius Marks Sanatorium; former President, Fayette County Medical Society and Kentucky Midland Medical Society; Member, Kentucky State Medical Association, Mississippi Valley Medical Association and American Medical Association; former Secretary and former Chairman of the Section on Medicine, Southern Medical Association; Councillor, American Clinical and Climatological Association; served during World War I as Major, Medical Corps, U. S. Army; Diplomate, American Board of Internal Medicine.

Dr. Bradley became a Fellow of the American College of Physicians in 1919, and served on the Board of Governors from 1925 until 1935, being Vice Chairman from 1930 to 1933 and Chairman, 1934-35. In 1935 he was selected as President-Elect as an outstanding example of an accomplished, outstanding internist without academic appointments. He served as President, 1936-37, and thereafter remained on the Board of Regents until 1940. He served on the Committee on Credentials from 1930 to 1940; on the Executive Committee, 1935-37; on the Committee on Public Relations, 1934-36; on the Consulting Committee on Annual Sessions, 1936-39; on the Committee on Future Policy for the Development of Internal Medicine, 1938-39; and on the Committee on Nominations, 1940-41.

Dr. Bradley's first important contribution was the development of a more extended and deeper interest on the part of members of the Board of Governors through his advocacy of a greater recognition and extension of the duties and authority of that Board. He was one of the early Governors who organized sectional meetings of members within his territory, and who promoted this activity among other Governors. One of his greatest contributions to the College was his work as a member of the Committee on Credentials, through disseminating a better understanding of the admission standards of the College among the several Governors and the clarification and rationalizing of admission regulations. The choice of Dr. Bradley as President was an indication that this College shall recognize outstanding practitioners of Internal Medicine, and that the Presidency shall not always be awarded to teachers, research workers and pure scholars—a recognition which met with wide approval among the Fellows. Shortly after his induction to the Presidency, the College moved into its present permanent home in Philadelphia. Also, during the early part of his Presidency, the American Board of Internal Medicine was established.

Further contributions made by Dr. Bradley during his Presidency, included: an appropriation of \$1,000.00 for the aid of the National Conference on Nomenclature of Disease; the establishment of a second Research Fellowship; a closer relationship between the Regents and Governors through the initiation of a joint dinner-meeting of the two Boards preceding the opening of each Annual Session; the establishment of the policy that the College membership should not be restricted wholly to Internal

Medicine, but should include the allied specialties; the establishment of a liaison committee to confer with the American College of Surgeons concerning matters of mutual interest; an amendment to the By-Laws providing for Alternate Governors for attendance at the Annual Sessions; the establishment of Roundtable and Panel Discussions on the Annual Session Programs; adoption of a proposal to prepare a History of the American College of Physicians, with appointment of Dr. William Gerry Morgan, M.A.C.P., as Historian.

At the 1947 Convocation at Chicago on April 30, a Mastership was conferred upon Dr. Bradley in recognition of his eminent career and his outstanding contributions to the College.

Although not unexpected, his death came as a great shock to his numerous friends, both in and out of the medical profession, but particularly in the American College of Physicians. His accomplishments richly entitled him to his many honors, but his warm handshake, his cheerful smile and manner, his sincerity and loyalty will longer be remembered and cherished even more than his achievements. New acquaintances soon became his devoted friends. Probably no one individual in the College made such a large number of loyal friends who loved him for his own delightful style of wit and humor, his companionship and his sound ideas for the betterment of the College.

It should be mentioned also that his great popularity was shared by his wife, Norma, who accompanied him on most of his trips to College meetings, encouraging him to the utmost in every way. Indeed, so much were they a part of one another that one usually heard not the name, Ernest, alone, but "Ernest and Norma." With Mr. Loveland, the Executive Secretary, and Mrs. Dowden, it was our sad privilege to visit Ernest only two days before his death. Even then, in his disorientation that so often precedes such passings, with his infectious cheerful smile, and recognizing all of us, he immediately began planning for our trip (this time by plane) to the College meeting in San Francisco. Shortly after he sank into his final sleep with a smile on his face, and passed on to his well deserved reward, without apparent suffering. He is gone, and those who had the great good fortune to know him (and "to know him was to love him") became better men and women for such a friendship. His creed is so well stated in the following verse by Van Dyke, entitled

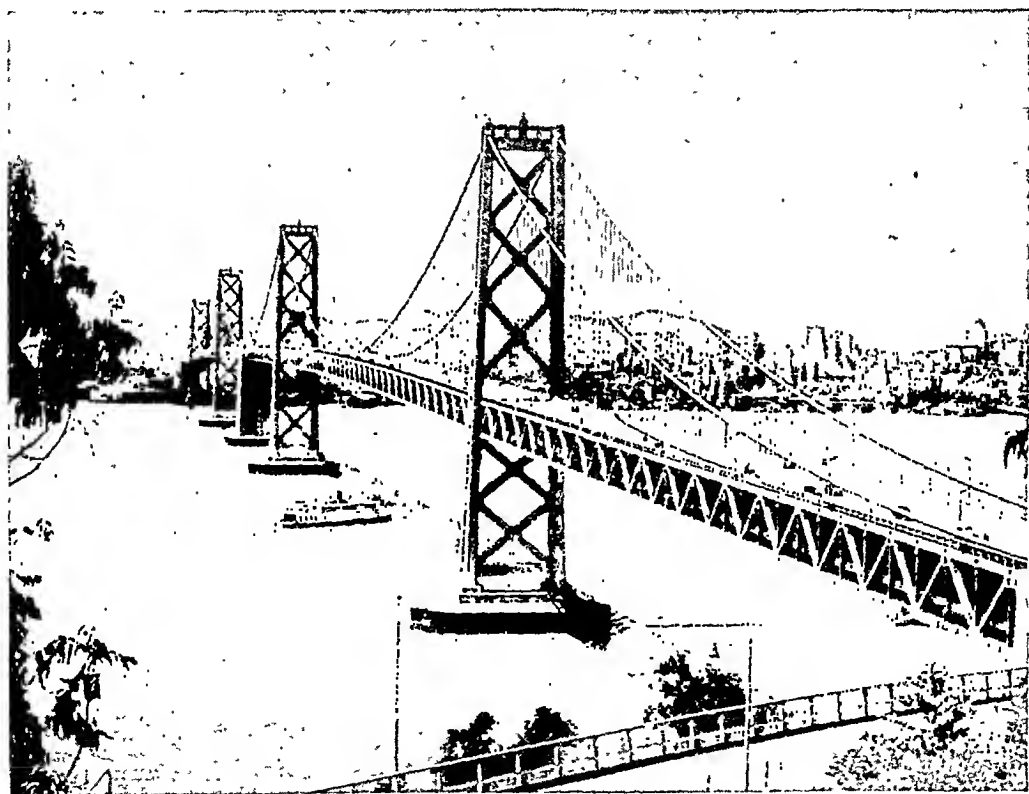
FOUR THINGS

Four things man must learn to do,
If he would make his record true,
To think without confusion clearly,
To act from honest motives purely,
To trust in God and Heaven securely.

—C. W. DOWDEN, M.D., F.A.C.P.,
Governor for Kentucky

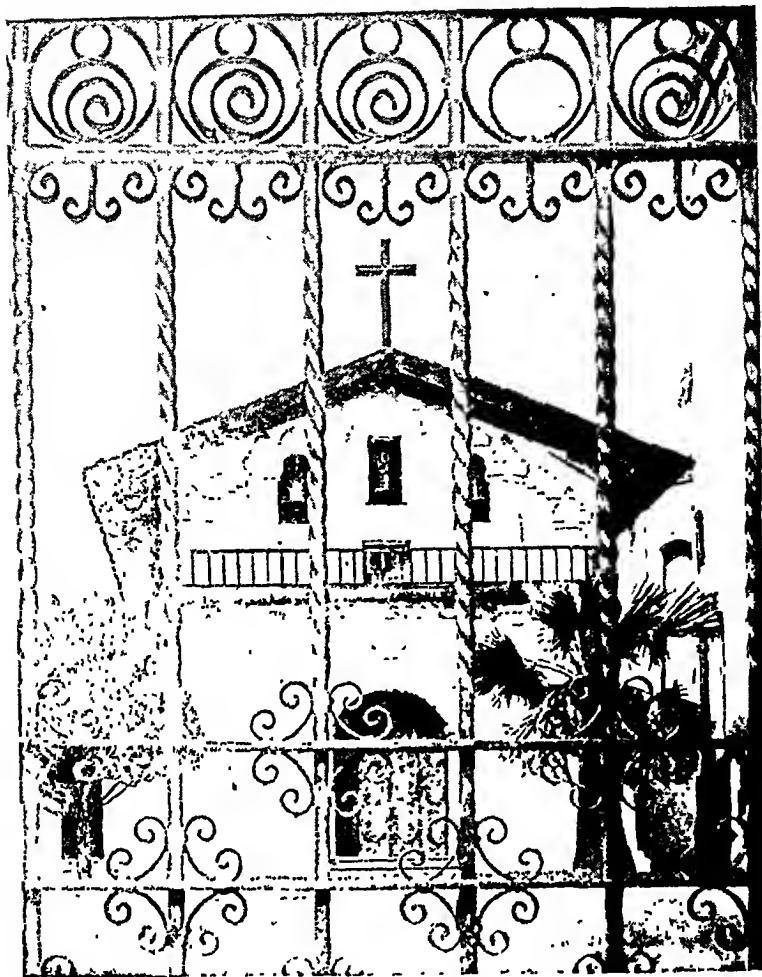
SAN FRANCISCO: SCENIC CITY AND MEDICAL CENTER A.C.P. MEETING PLACE APRIL 19-23, 1948

"California, here we come!" This slogan of the Argonauts of the "gold rush" days is today, approximately one hundred years later, changed to "San Francisco, here we come!" The occasion of the present slogan is due to two simultaneous events: the Twenty-ninth Annual Session of the American College of Physicians, and the Centenary of the Discovery of Gold. Many descendants of those pioneers who came for gold will come this year not for gold as a yellow metal, but to behold the miracle wrought by time in California, and to seek the easily uncovered "pearls of wisdom" which lure Fellows and Associates to the annual meetings of the American College of Physicians.



The San Francisco-Oakland Bay Bridge.

San Francisco is located on a peninsula six by seven miles in area, and looks down on a landlocked harbor 453 square miles in extent. The charm of the city and its surroundings is well known, but it will not be amiss to mention briefly some of its important historical features.



Mission Dolores—The church where San Francisco was born.

The old Mission Dolores stands at Mission and Sixteenth Streets. Once considered "out in the country," it is now in the heart of the city. Founded by the Padres in the eventful year of 1776, the mission was actually built by Indians who baked the soil into adobe bricks and fastened the beams together with wet rawhide thongs. It has been restored as need has arisen, and is open to visitors.

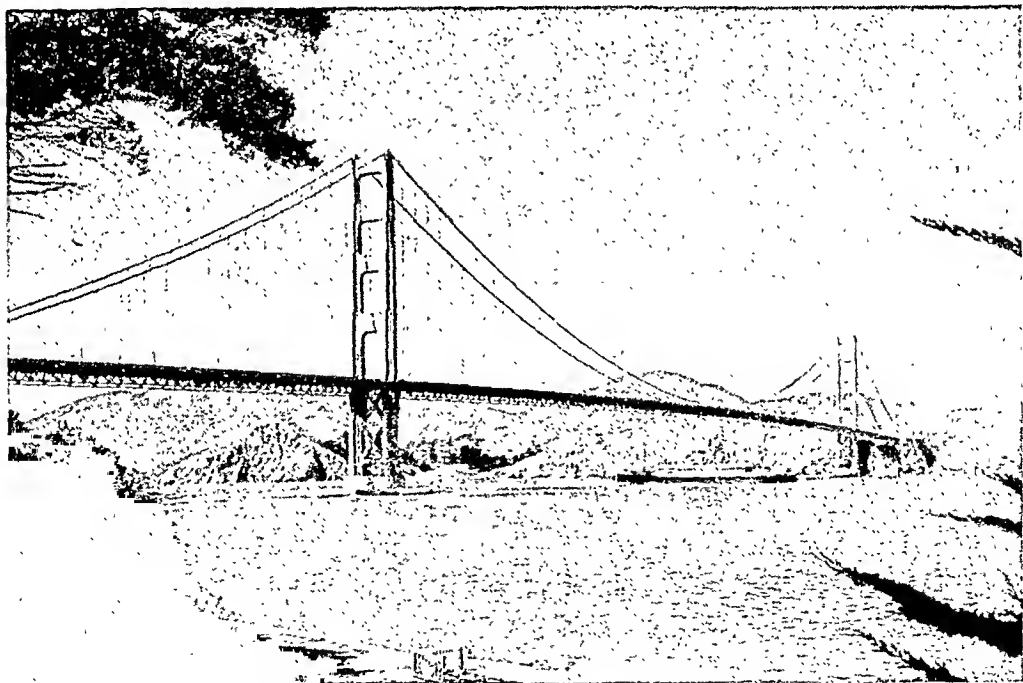
The Presidio of San Francisco, now occupied by the United States Army, was once the fort and the home of the Spaniards. In 1769 they discovered the Golden Gate and its magnificent bay, adding California to the Province of Mexico. This area was administered by a governor sent from Mexico. General Vallejo, the last of the Mexican governors, is honored and remembered by Californians today.

It was at the Presidio that the Russian, Nikolai Petrovich de Rezanov, courted and won the beautiful Doña Maria Conception Arguello, daughter of the Commandante. Rezanov perished on his long journey back to Moscow, and so was never able to claim his bride or build the coastal trading center of which he had dreamed. In grief over the loss of her lover, Doña Concha

joined a holy order, and, as Sister Dominica, was finally laid to rest at Mission Dolores.

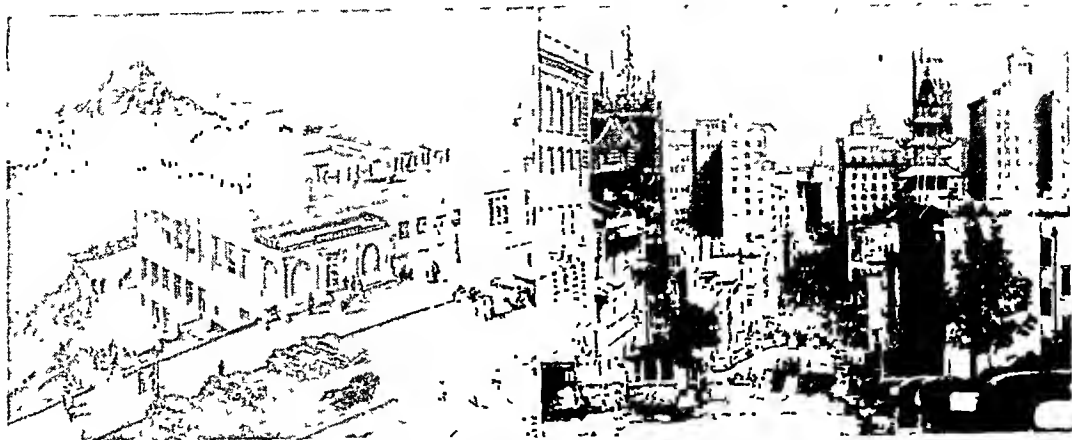
Just two blocks from Union Square and an equal distance from the financial district is Chinatown with its century old exemplification of the culture of the Orient. Its many shops and Chinese restaurants are part of the itinerary of nearly all travelers to San Francisco. This is the largest Chinese community outside of China.

In the earlier years of the city the coming and going of ships was one of the main outside interests of San Franciscans. Vessels from all over the world, China, Japan, India, New York, came with immigrants and goods for trade. Today when one visits the Embarcadero to see the cargoes that come and go, gold is not in evidence as it was in '49, but wealth and the atmosphere of far and distant places still accompany the vessels that slip into the harbor through the Golden Gate, passing under the Golden Gate Bridge, the longest and tallest single-span suspension bridge in the world. From the Embarcadero one can view the San Francisco-Oakland Bay Bridge, which stands without a rival as to length, the total span being eight and one quarter miles.



A ship passing under the Golden Gate Bridge on its way out the Golden Gate into the Pacific.

Just beyond the Embarcadero is Fisherman's wharf. Here the fishing craft swing at anchor while the day's catch is unloaded. Shrimp and crayfish are cooked in large kettles in front of the many restaurants on the wharf. The well filled tables inside attest the psychological advantage of this form of advertising fresh sea food. As you leave Fisherman's wharf and arrive at the foot of Powell Street, you will find one of the historic cable cars being



Cliff House with the seals disporting themselves on the rocks only a few hundred yards from shore.

California street cable car climbing one of San Francisco's hills.

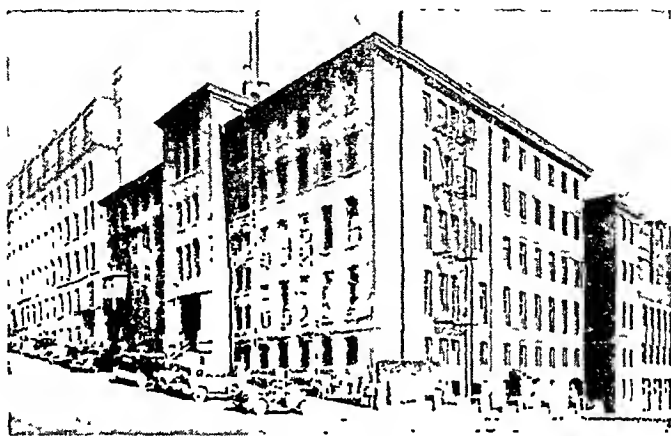
spun around on a turntable in preparation for its return trip through the heart of the city. While the car clang-clangs up the hills you will cling to your seat. On top of Nob Hill a beautiful view of the harbor and bay unfolds itself and one forgets the uneasiness of the perpendicular ascent.

There remains still our Golden Gate Park, an important feature of San Francisco that all visitors will want to see. This area was once barren sand dunes stretching between the city and the ocean. In 1873, The Santa Clara "Democrat" wrote, "Of all the white elephants the city of San Francisco ever owned, they now have the largest and heaviest in the shape of 'Golden Gate Park'—a dreary waste of shifting sand hills where a blade of grass cannot be raised without four posts to support it and keep it from blowing away." The dunes continued to shift until 1887, when John McLaren, a Scotchman of indomitable will and keen foresight, was put in charge. In his more than fifty years of service, "Uncle John" planted more than a million trees and made the barren dunes into one of the world's most beautiful parks.

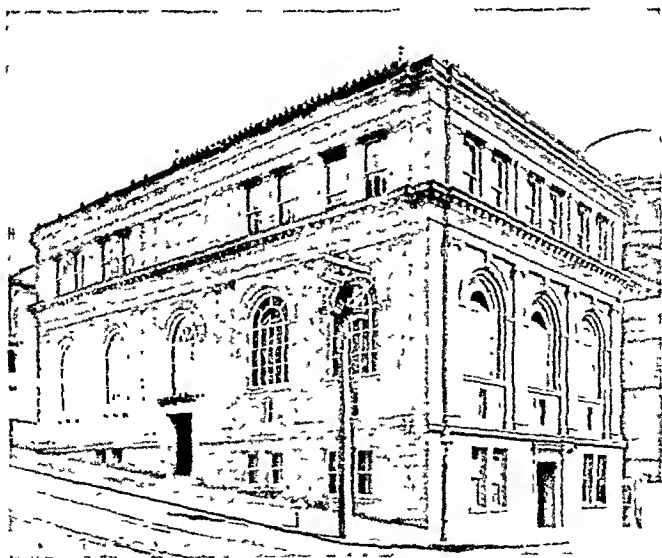
California is about to celebrate three centennial years: 1948, the Gold Discovery; 1949, the Gold Rush; and 1950, Statehood. January 24th, 1948, marks exactly one hundred years since James W. Marshall discovered gold at Sutter's new sawmill at Coloma on the American River. On this day Californians, led by Governor Earl Warren, will hold a ceremony at the James Marshall gold discovery site at Coloma. It is planned to introduce features reminiscent of the days of the gold discovery in connection with the coming meeting of the American College of Physicians, April 19 to 23.

For the past fifty years or more, San Francisco may be said to have enjoyed a uniform acceleration in the medical fields of research, teaching, and hospital services, due to expanding opportunities for development of medical education and public health. The past thirty-five years in particular have been fruitful in research at the Stanford University School of Medicine, the Hooper Foundation for Medical Research, and the University of California. The latter institution has more recently gained world-wide recognition

through the elaboration of the cyclotron by Ernest Lawrence of the Physics Department in Berkeley, California. This gave impetus to the study of nuclear physics and resulted in the production of radioactive compounds for use in research and the treatment of disease, both in Berkeley and at the University of California Medical School in San Francisco. The Biophysics Department has provided isotopes for intensive investigation of disease in the domain of animal and plant life, thus opening up fields of research undreamed of a half century ago.



Lane and Stanford University Hospitals.



Lane Medical Library, Stanford University School of Medicine.

San Francisco has two class A medical schools: Stanford University School of Medicine and the University of California Medical School.

The Medical Department of the University of the Pacific was the first medical college on the Pacific Coast. Founded by Elias Samuel Cooper in San Francisco in 1858, it was discontinued in 1864, reorganized six years

later, and affiliated with University College in 1872 under the name of the Medical College of the Pacific. These colleges were succeeded in 1882 by Cooper Medical College, incorporated by Dr. Levi Cooper Lane and named in honor of his uncle, Dr. Elias Samuel Cooper.

In 1882 Dr. Lane built the first of the present college buildings in San Francisco, on land donated by himself. Further gifts of Dr. Lane include Lane Hospital (1894), the Lane Medical Lectureship (1896), and provision for a library building.

Under permission granted by Dr. Lane, the Cooper Medical College was transferred to Leland Stanford Junior University in 1908. The main buildings in San Francisco consist of the Clinical and Laboratory Building, the Ruth Lucie Stern Research Laboratory, Lane Hospital with a capacity of 180 beds, and the Stanford University Hospital with about 130 beds. The Lane Medical Library is housed in a separate building erected in 1912, opposite the Clinical and Laboratory Building. This is the largest medical library west of Chicago and contains over 108,000 volumes. It has become a center for library service throughout the entire Pacific Coast region.

The laboratories of Anatomy, Bacteriology and Experimental Pathology, Chemistry and Physiology are located on the Campus at Stanford University, thirty miles southeast of San Francisco, adjoining the city of Palo Alto.

The entering class in the Medical School is limited to sixty students. The course is four years but all students are required to take a fifth year (interne year) before receiving the degree of Doctor of Medicine. The School of Medicine, in coöperation with the San Francisco Department of Health, controls about 500 beds in the San Francisco Hospital.

The history of the development of the University of California Medical School had its inception in 1864 when Dr. H. H. Toland erected a building in San Francisco to serve as a center for a medical school. In 1873 this building, then known as Toland Hall, was transferred to the Regents as a department of the University of California. The medical faculty controlled the policy of the school, and its support was derived from fees collected from the students. In 1898 the school was moved to its present situation on Parnassus Heights, where the late Adolph Sutro had given thirteen and one-half acres of land to the University. The Regents, in 1902, passed a resolution which made the Medical Department an integral part of the University. The properties of the school were transferred to the University of California and full support of the school was assumed by the Regents. Suitable laboratories were equipped and the first two years of medicine were put on an academic basis. The earthquake and fire of 1906 destroyed the Out-patient Department, necessitating transfer of the work of the first two years to Berkeley. The main building of the school was changed into a hospital and out-patient clinic.

In 1915 an affiliation was made with the Hospital for Children and Training School for Nurses, and in the same year elective courses in Homeopathic Therapeutics were included in the curriculum.

The present University of California Hospital was completed in 1917; two years later a Nurses' Home was erected across Parnassus Avenue from the hospital. In 1933 a new out-patient building attached to the hospital was opened; in 1928 laboratories for the teaching of Bacteriology and Pharmacology were provided on the San Francisco Campus. At Berkeley the divisions of Anatomy, Biochemistry and Physiology are housed in the Life Sciences Building, which was completed in 1930.

Plans are completed and the funds provided by the State Legislature for a new University Hospital and a Medical Sciences Building, which will be erected at the Medical Center in San Francisco in the near future.

The Langley Porter Clinic, a part of the Department of Institutions of the State of California, was opened in 1942. Situated at the Medical Center, this building is a 100-bed research and teaching institute for psychiatry, erected by the Department of Mental Hygiene of the State of California with the provision that the research and teaching functions of the Hospital shall be carried on under the direction of the University of California Medical School. The clinic includes an operating room, x-ray laboratory, a laboratory for electroencephalography, and an occupational therapy department.



Airplane view of The University of California Medical Center.

1. New Out-patient Department Building.
2. University Hospital.
3. Laboratories Building (Preclinical Departments).
4. School of Pharmacy.
5. Hooper Institute for Medical Research.
6. Nurses' Home.

Through the generosity of the Commonwealth Fund of New York City, a child guidance clinic and studies in child psychiatry were instituted.

The University Hospital has a capacity of more than 300 beds. It is essentially for teaching and, through support from the State of California and from endowment funds, a certain number of free beds are available. Such patients come from various parts of California and the Pacific Coast. The San Francisco Hospital is a municipal hospital built in 1915 at a cost of \$3,500,000, operated by the Board of Health of the City and County of San Francisco for citizens unable to pay for hospital care. There is a main group of 21 occupied wards, a Tuberculosis Department of twelve occupied wards and an Isolation Department of four wards. About 380 beds in the main group and 200 beds in the Tuberculosis Department are assigned to the University of California Medical School. The Psychopathic Department is equipped to care for 100 patients, and the Maternity Department cares for 125 patients. These services are divided between the two University medical schools, Stanford and California.

The Laguna Honda Home is an adjunct of the San Francisco Hospital. It houses approximately 1,900 persons, 800 of whom are confined to the infirmary provided for the care of the aged and chronically ill. The infirmary is a modern hospital with nineteen wards. It has an excellently equipped surgery, x-ray department, laboratory and morgue. A small outpatient clinic is provided for ambulatory cases. The University of California Medical School supervises the medical care of the patients in return for teaching and clinic privileges.

In January, 1947, the Laboratory of Experimental Oncology was established as a coöperative project in connection with cancer research. This laboratory is housed in the Laguna Honda Home and contains electrophysiologic equipment for the study of physiology in cancer patients, a biochemical-immunologic unit, and an animal colony. An experimental ward of 25 beds has been established. This laboratory is a joint project of the

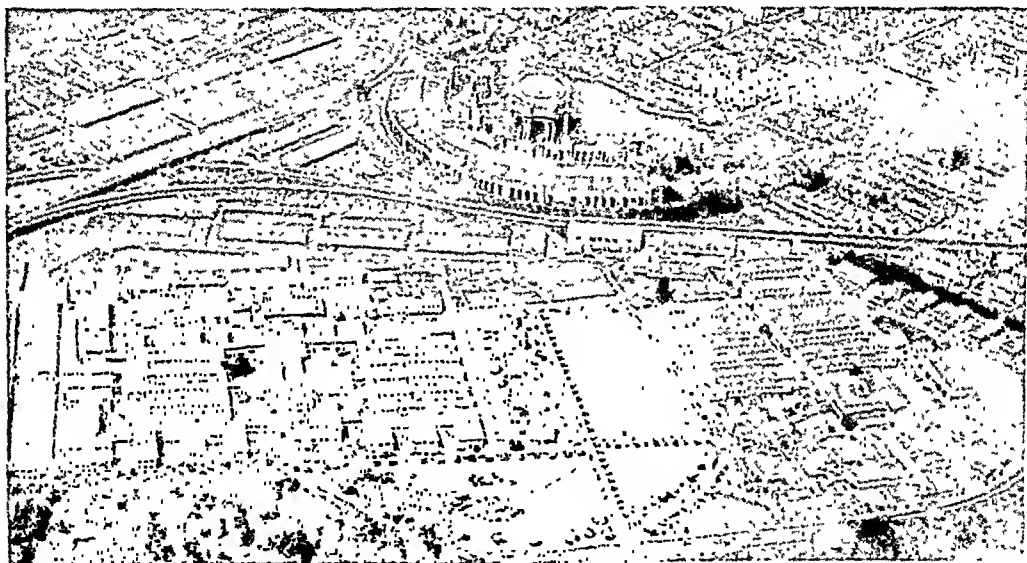


The George Williams Hooper Institute for Medical Research, University of California Medical School.

University of California Medical School, the National Cancer Institute, National Institute of Health, United States Public Health Service, and the Department of Public Health, City and County of San Francisco.

In 1913 Mrs. George Williams Hooper presented certain valuable property to the Regents of the University of California for the founding of an institute of medical research, known as The George Williams Hooper Institute for Medical Research, in memory of her husband, a pioneer citizen of San Francisco. A Board of Trustees conferring with the Regents determines the policy of The George Williams Hooper Foundation, and its work is closely correlated with that of the Medical School.

In addition to the hospitals connected with our two medical schools, there are some sixteen hospitals in the city proper, and several Class A hospitals in the Bay Area and peninsula cities adjoining San Francisco.



Airplane view of Letterman General Hospital, Presidio of San Francisco.

Located in the Presidio of San Francisco is the Letterman General Hospital, one of the larger Army hospitals of the United States. It was organized in 1898 during the Spanish-American War. In 1900 a permanent hospital was completed to accommodate 380 patients. During World War I, in 1917 and 1918, the hospital was greatly enlarged. Since 1941 further expansion has become necessary because of the great demands placed on the institution by World War II. All of the specialties are well organized in this hospital; the ability and standards of the medical officers in charge of the departments and services are of a high order. A new development resulting from the last war is a center for amputees occupying a portion of the hospital. The Occupational Therapy Department is an especially notable and valuable adjunct in the rehabilitation work, which is such an important feature of this institution.

The Veterans Administration Hospital, known as Fort Miley, has a beautiful location overlooking the Golden Gate and the Lincoln Heights Municipal Golf Course. Built in 1934, it has 356 beds for general medical and surgical cases; reconstruction under way will add approximately 75 beds and new laboratories including deep roentgen therapy. The medical service is under the direction of the Deans' Committee, composed of members from the medical schools of the Universities, Stanford and California. This institution is a diagnostic center, admitting problem cases from other western states. In addition to the regular attending staff there are 47 residents in training at present.

Practically every seaport city has a Marine Hospital, but San Francisco has an especially efficient and well-staffed Marine Hospital of about 400 beds, which has an adequate equipment and a reputation for high quality of medical care. The capacity of the institution was considerably increased during the late War, to about 500 beds, in order to care for the Coast Guard, Maritime Training Schools and Merchant Marine. The hospital is accredited for the training of internes and residents.



Franklin Hospital.

There are four important hospitals operated by Sisters of Catholic Orders, in San Francisco. St. Mary's Hospital, the oldest Catholic Hospital in California, was founded by the Sisters of Mercy in 1857. Today it has a Class A rating, supports 375 beds, has 10 internes and 12 residents.

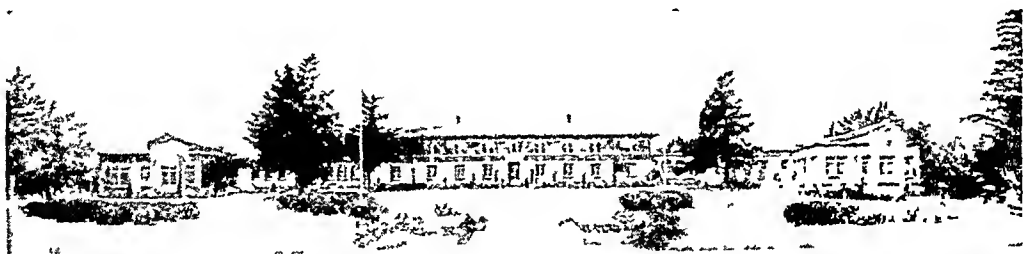
St. Joseph's Hospital was founded by the Franciscan Sisters of the Sacred Heart in 1892. In 1928 a new, modern hospital building was erected on the site of the original hospital. This institution is a Class A general hospital of 235 beds and 45 bassinets.

Mary's Help Hospital is conducted by the Sisters of Charity of St. Vincent de Paul. It was founded in 1906, but was destroyed by the earthquake and fire of that year, and was rebuilt in 1912. Mary's Help is a general hospital, approved by the Council on Medical Education and Hospitals of the

American Medical Association. It has 200 beds, an Out-patient Department, School of Nursing, Cancer Detection Clinic, Pediatrics Department and Physiotherapy Department.

More recently the Sisters of Mercy have taken over the former Dante Sanatorium, which under the original name of the Adler Sanatorium, was for many years the mecca in time of illness of the socially and financially elect of San Francisco. Among the important features were the impeccable trays served to those able to partake of food. During the recent war it was utilized by the Army as a convalescent hospital. On November 4, 1946, the Sisters of Mercy reopened it under the name of the Notre Dame Hospital, for the care of patients suffering from internal medical ailments. The capacity at present is 175 beds.

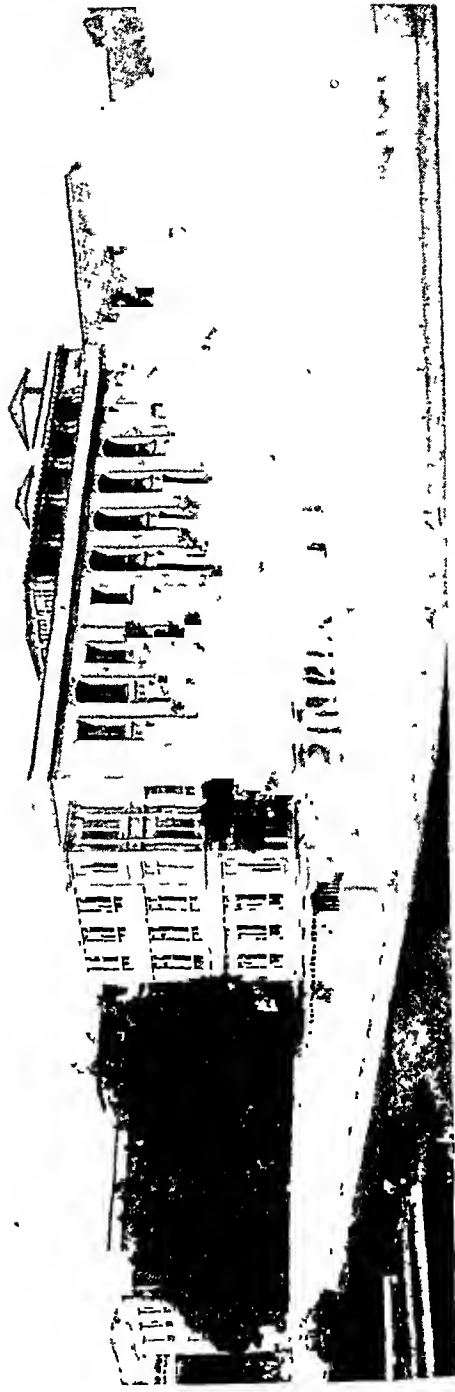
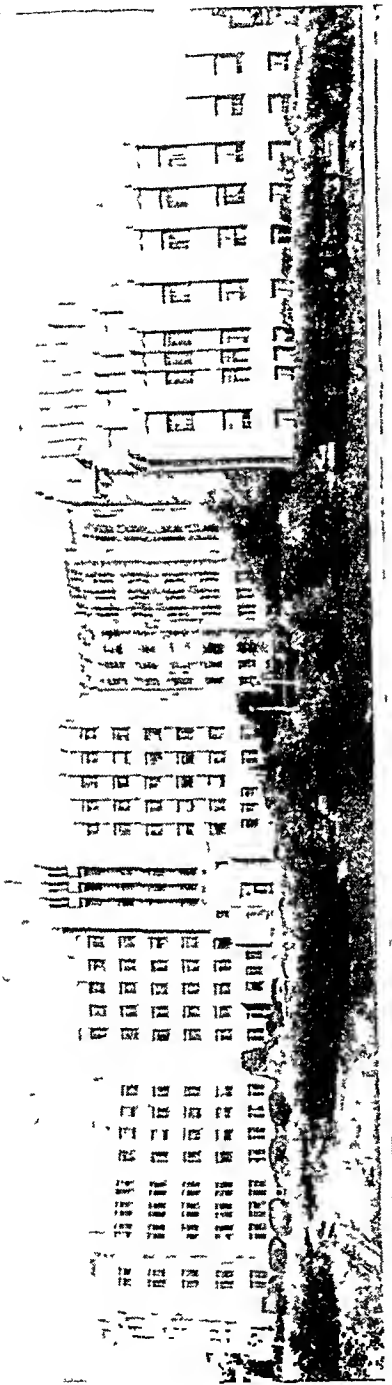
Two hospitals, the French and the Franklin, were built and operated by the French and the German Benevolent Societies, respectively. The former is a modern and complete hospital of approximately 250 beds. The Franklin Hospital was founded in 1852; the present structure was built in 1908 but has been extensively improved and re-equipped since 1939. The hospital has been approved by the American College of Surgeons and the American Medical Association for graduate training in the medical and surgical specialties.



Shriners Hospital for Crippled Children

St. Luke's Hospital was founded in 1871 by the Reverend Thomas Woodley Brotherton, M.D., D.D., who received his medical training in Baltimore, and came to California in 1849. The present buildings were erected in 1911, but the medical staff of the hospital was well organized and held regular meetings for several years previous to 1911. The staff rosters contained the names of men who were outstanding pioneers in medicine in San Francisco. The hospital is operated under the auspices of the Episcopal Diocese of California. It also is Council-approved for the training of internes and residents, and operates an accredited School of Nursing. About 230 beds are available in this general hospital.

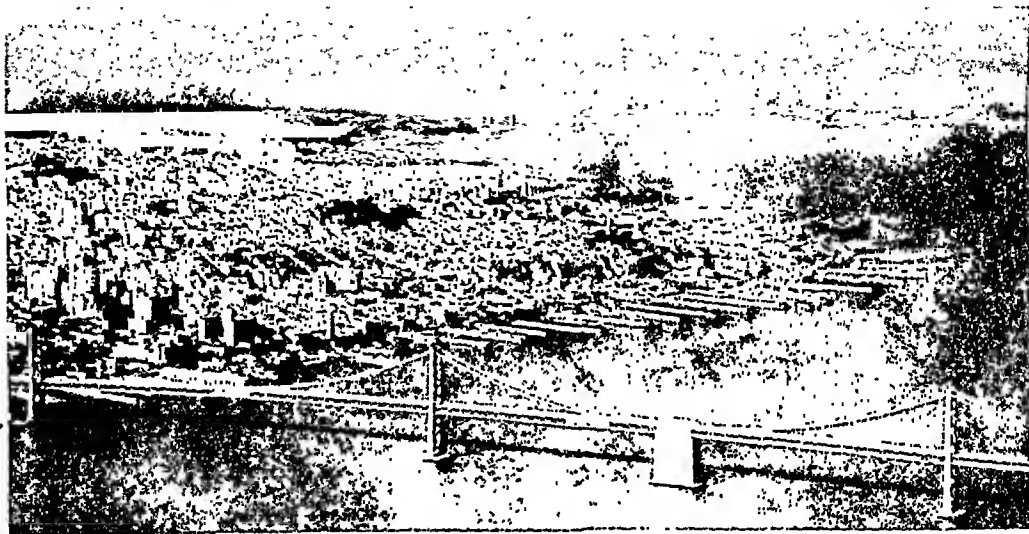
The Southern Pacific General Hospital is an institution of 450 beds, serving approximately ninety thousand employees of the Southern Pacific Railroad Lines. It is a diagnostic center for medical problems and has complete services in all of the specialties. The hospital is accredited for graduate



Top: Veterans Administration (Fort Miley) Hospital
Bottom St. Luke's Hospital

training in internal medicine and general surgery. About 7,500 patients are treated in the hospital annually, together with a large number of patients treated in the Out-patient Department.

The Mount Zion Hospital is a general hospital of about 150 beds, operated by the Federated Jewish Charities of San Francisco. A large number of beds are available for charity patients. In 1931 and subsequently, special research and laboratory facilities have been added. The present hospital was built in 1912; preparations are under way at this time to construct a large, new addition.



San Francisco by the Golden Gate.

San Francisco was one of the cities selected by the Ancient Arabic Order, Nobles of the Mystic Shrine, for erection of a Hospital for Crippled Children. This hospital has a beautiful setting, accommodates 60 patients, with a turn-over of about 300 beds per year. Children are able to continue their school work while under treatment, through the coöperation of the Board of Education. The hospital is accredited and has two orthopedic residents and one in pediatrics. There is an affiliation with the University of California Medical School for teaching purposes.

The Hospital for Children and Training School for Nurses has been mentioned as an affiliated hospital of the University of California Medical School. Founded in 1875, it has a present capacity of about 300 beds. An important feature of this hospital is a wing devoted entirely to the care and treatment of communicable diseases. The maternity department and the orthopedic section are also important features of the hospital.

This survey would be incomplete without the mention of San Francisco's vigorous and puissant County Medical Society, which has about 1300 active members. Organized in 1870, the Society purchased its own home on Washington Street in 1926. The large reference library of about 13,000

volumes will shortly be distributed to the libraries of the two medical schools. It will be interesting and inspiring (beautiful view) for members of the American College of Physicians to visit the Society's building. It was formerly one of the more pretentious mansions occupied by a pioneer San Francisco family.

Note: Material, including photographs, supplied by the San Francisco Convention and Tourist Bureau and Californians Incorporated, is gratefully acknowledged.

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RENAL DISEASES: SOME FACTS AND PROBLEMS *

By LOUIS LEITER, M.D., Ph.D., *New York, N. Y.*

THIS discussion will include some comments on the classification of renal diseases; the pathogenesis and prognosis of acute diffuse glomerulonephritis; the sequence of events in hypertensive vascular disease or "essential" hypertension, and some of the diagnostic and therapeutic implications; the status of diabetic glomerulosclerosis; and the rôle of the great group of functional diseases of the kidney with special emphasis on circulatory or hemodynamic disturbances, as well as on affections of the renal tubules. Obviously, only the highlights of these major aspects of the field of organic renal disease and dysfunction can be covered.

CLASSIFICATION

You will notice that the classification of organic medical renal diseases (table 1) follows generally the accepted views of Volhard and Fahr,¹ Fish-

TABLE I

Classification

A. Organic Renal Diseases

1. Glomerulonephritis—Acute; chronic
2. Glomerulonephrosis—Lipoid; amyloid
3. Glomerulosclerosis—Arteriolar; diabetic
4. Glomerulitis—Toxic; embolic; thrombotic; allergic
5. Pyelonephritis—Acute; chronic
6. Vascular—Arteriosclerotic; inflammatory (allergic)
7. Tubular—Necrotizing; obstructive; degenerative
8. Congenital anomalies

berg,² Addis and Oliver,³ and Bell.⁴ For the sake of convenience in thinking about pathogenesis and clinical syndromes, I have rearranged the grouping somewhat,⁵ e.g., in classifying lipoid nephrosis as a glomerular rather than

* Presented May 1, 1947 as part of a symposium on kidney diseases at the Michael Reese Hospital, Chicago, in connection with the 28th Annual Session of the American College of Physicians.

From the Medical Division, Montefiore Hospital, New York.

tubular disease since abnormal glomerular permeability to plasma protein is probably the primary defect in this disease. For similar reasons, amyloid renal disease is included under the same heading and, perhaps, the specific toxemia of pregnancy may also be classified under glomerulonephrosis although the present working classification will probably have to be modified as soon as we learn more about the rôle of steroid hormones, their site of origin and their chief site of action in the body in relation to the edema and hypertension of the toxemia of pregnancy.

In the case of the organic vascular diseases of the kidney (among which embolism and thrombosis should be included) there is some duplication in the classification because of the desirable emphasis on glomerular involvement in the form of glomerulosclerosis. This distinction is not merely a pathological one but has definite clinical implications in regard to urinary changes and impairment of renal function. Our present methods of diagnosis with the possible exception of the estimation of renal blood flow and filtration fraction⁶ in subjects without cardiac failure, are not sufficiently sensitive to detect renal vascular disease before glomerular changes have developed; hence, when we make a diagnosis of renal arterio- or arteriolosclerosis, benign nephrosclerosis, hypertensive renal vascular disease or arteriosclerotic Bright's disease—whichever designation you prefer—we really mean glomerular sclerosis associated with, or secondary to, hypertensive disease. To be sure, this change in the glomerular vasculature is bound to reflect itself in functional and, later, organic changes in the corresponding tubules, because of the arrangement of the renal circulation.

You will observe that the term "glomerulitis" has been substituted for "glomerulonephritis" to cover the focal toxic, embolic, thrombotic or allergic inflammatory lesions of the glomeruli, and that this whole group has been separated from glomerulonephritis. This leaves us without the clinical diagnosis of "focal glomerulonephritis," popular in many quarters. I believe that there is now considerable evidence, clinical and pathological, to make the use of the diagnosis of "focal glomerulonephritis" very dangerous from the standpoint of both treatment and prognosis.

Clinical experience has shown that the Volhard and Fahr¹ concept of focal glomerulonephritis was based partly on inadequate follow-up of patients, on underestimation of the significance of the urinary findings in the so-called latent stage of nephritis, and certainly on a somewhat dogmatic a priori concept of the cardinal symptoms of acute diffuse glomerulonephritis. If we assume with Volhard that hypertension is an absolute *sine qua non* of acute diffuse nephritis, then, of course, many cases of mild diffuse nephritis but without hypertension, edema or gross renal impairment will be misdiagnosed as focal glomerulonephritis. Careful follow-up on such cases with adequate study of urinary sediment and renal function has disclosed a distressing proportion of persistent nephritis which, after some or many years, finally resulted in the typical end-stages of diffuse glomerulonephritis.

Furthermore, Chabanier and his associates⁷ made biopsies on the kidneys of a significant number of patients with various types of glomerulonephritis; all with an alleged focal nephritis revealed typical diffuse glomerular inflammation, indistinguishable from the lesion found in a parallel series of patients with the clinical picture of diffuse nephritis of the Volhard and Fahr classification. One should be particularly skeptical of the diagnosis of recurrent focal nephritis in view of the prevalence of exacerbation of diffuse glomerulonephritis during upper respiratory infections.

Furthermore, the diagnosis of focal nephritis when based on albuminuria and hematuria discovered during or after an acute infection, always carries with it the hazard of overlooking the numerous and important urologic causes of gross or microscopic hematuria. It is for these and other cogent reasons that a clinical diagnosis of focal glomerulonephritis should never be made. If there are red blood cell casts in the urine, the source of the hematuria must be glomerular and the differential diagnosis will then include the various causes of glomerulitis. Obviously, the entire clinical picture of the underlying disease must be taken into account. On the other hand, in certain obscure conditions the demonstration of urinary changes compatible with glomerulitis may settle the diagnosis in favor, let us say, of allergic vascular disease, visceral lupus erythematosus or subacute bacterial endocarditis.

ACUTE GLOMERULONEPHRITIS

A. Immunology. Just a few remarks on the nature of the immunological reactions which lead up to the development of acute diffuse glomerulonephritis in man. The overwhelming association with hemolytic streptococcal infections⁸; the latent period between the acute infection and the onset of acute nephritis; the permanent immunity to nephritis after recovery on the one hand⁹ and the persistent allergic reaction of the kidneys to reinfection with hemolytic streptococci in the less fortunate group that fails to heal after the initial attack¹⁰; and, finally, the experimental production of acute diffuse glomerulonephritis in laboratory animals by the Masugi¹¹ method of developing antibody to kidney protein, although in a foreign species—all this evidence points strongly, if not conclusively, to the theory that acute nephritis in man represents an allergic reaction occurring in the kidneys, presumably as the result of an auto-immune response to kidney protein rendered antigenic by the toxic or denaturant action of some streptococcal product, or combined streptococcal-tissue product, as suggested by Schwentker and Comptoier.¹² A combined or complex auto-antigen resulting from a sulfa drug and kidney protein may similarly be responsible for the polyarteritic or periarteritic nodosa-like lesions produced in rabbit kidneys by Rich,¹³ and found in some human kidneys after sulfa treatment. The analogy can be broadened to include many of the cases of glomerulitis occurring during generalized diseases of presumably allergic origin.

However, it should be noted that even the Masugi nephritis is not necessarily the simple kidney antigen-kidney antibody reaction, as has been well pointed out by Kay¹⁴ in experiments on rabbits. He explains the latent period of the Masugi reaction on the basis of secondary antibody formation to foreign serum protein. Actually it is impossible to produce anti-kidney antibodies in the same species by Masugi technic. According to the Caveltis¹⁵ the kidney acts as a hapten and the streptococcus as the protein carrier in the auto-antibody response which they have reproduced for the first time (table 2). The human situation may also be far more complex

TABLE II

Immunologic Mechanism of Glomerulonephritis

A. Experimental:

1. *Masugi's heterologous "nephrotoxin":*
Kidney antigen \rightarrow anti-kidney serum
Anti-kidney serum + kidney \rightarrow allergic nephritis
2. *Kay's explanation of process:*
Rabbit kidney antigen \rightarrow duck anti-kidney serum
Duck anti-kidney antibody + rabbit kidney \rightarrow harmless complex (H.C.)
Normal duck serum antigen \rightarrow rabbit anti-duck antibody
Rabbit anti-duck antibody + H.C. in rabbit's kidney \rightarrow allergic nephritis
3. *Caveltis' effective mechanism:*
Streptococcus + kidney = complex auto-antigen
Auto-antigen \rightarrow anti-kidney auto-antibody
Auto-antigen + auto-antibody \rightarrow nephritis

B. Human: As in A3, first suggested by Schwentker and Comploier

than is ordinarily assumed, and, until more direct evidence is obtained as to the nature of the antigen and antibody involved in this remarkable reaction, final judgment must be withheld.

We are still a long way off from preventing acute glomerulonephritis by the administration of some anti-histaminic agent. It is not even certain whether the very early administration of adequate doses of sulfa or penicillin in acute streptococcal upper respiratory infections diminishes the small incidence of acute diffuse nephritis. It is very difficult to obtain reliable statistical material on this subject.

The rôle of diet in the treatment of acute glomerulonephritis may also be considered from the immunological viewpoint if one bears in mind Cannon's¹⁶ experiments on the influence of dietary protein on the formation of antibodies. Conceivably, any measure which sharply reduces or suppresses the ability of the body to respond to an antigen may, to this degree, reduce the extent of the anaphylactic reaction that depends on the combination of so much antibody with so much antigen. A very low protein diet early in acute nephritis may retard the formation and accumulation of sufficient antibody to maintain the dangerous level of the allergic reaction in the kidney. On the other hand, simultaneous suppression of antigen formation by early

chemotherapeutic inhibition of bacterial growth will also help in reducing the reactant substances. It is obvious that little can be expected on this basis from therapeutic dietary restriction after the glomerulonephritis has been well established. Addis¹⁷ has long claimed that the fate of the patient with acute nephritis, insofar as renal recovery is concerned, is settled within the first week or two. Protein in the diet during this period may well have more far reaching effects than simple reduction of renal excretory work. But all this is largely speculation and more facts are needed.

B. Diagnosis. The importance of an early diagnosis of acute nephritis cannot be overestimated. A simple consideration of the sequence of events between the onset of the bacterial infection and the occurrence of acute nephritic symptoms or signs indicates clearly that it is the duty of the physician to examine the urine carefully at intervals of one, two and three weeks after the onset of acute streptococcal infections. The usual analysis of the urine obtained at the first visit, at the height of the infection, is of value only as a control specimen and to detect the occasional case of mild chronic active or latent glomerulonephritis acquired at some time in the past. It must be emphasized that concentrated urine specimens should be obtained after 12 to 18 hours of dehydration, and that centrifugation is essential. Under these conditions, minor transitory urinary changes may be detected at the right interval (one to three weeks after the beginning of the acute infection) in 5 to 10 per cent of young individuals with proved hemolytic streptococcal infections. Perhaps only 1 per cent will develop clinical acute diffuse glomerulonephritis. It is the failure to test the urine at the right time that permits the accumulation of instances of chronic glomerulonephritis of so-called idiopathic or insidious onset. Acute and chronic glomerulonephritis have the same etiology, but it is unrecognized or overlooked in the latter, due largely to lack of obvious symptoms in the vast majority of post-infectious acute nephritis. I do not believe that there is a non-specific chronic nephritis in children, as Aldrich¹⁸ has claimed. It is rather the result of an undetected, mild but unhealed, acute nephritis. The story of scarlet fever acute nephritis with its practically non-existent chronic form is valuable evidence in favor of this view.¹⁹

C. Prognosis. There has been a great variety of opinion concerning the prognosis of acute glomerulonephritis with a typical clinical syndrome. In some series as high as 70 or 80 per cent of the cases progressed into a chronic irreversible stage; in other series, almost 90 per cent recovered completely and, presumably, permanently. One of the great difficulties in evaluating much of the data in the literature is the means of distinction between the initial acute nephritis and exacerbations, during some infection, of previously unrecognized chronic nephritis. Another problem has been the nature of the follow-up examination. When the Addis sediment count was first popularized, the prognosis of acute nephritis suddenly became very gloomy, even in children, in California.²⁰ The same method used in New York by the same

author gave no such dire results.²¹ One of the reasons for this difference must have been the nature of the clinical material in the California clinic. Many of the cases were probably unhealed or reactivated glomerulonephritis, without control observations prior to their admission to the hospital; hence the prognosis was much poorer than in patients seen during the initial acute nephritis. Some of the patients may have been selectively referred for examination because they were not doing well, while the recovered group remained at large, and outside of the statistics. These and other points are well discussed in a recent review by Rudebeck,²² whose own data are illustrated in table 3.

TABLE III
Prognosis of Acute Post-Infectious Glomerulonephritis *
(J. Rudebeck, *Acta med. Scand.*, 1946)

		%
Total patients (ages 11-67) (admitted within 3 mos. of onset)	318	100.0
Deaths, acute or subacute	21	6.6
Chronic nephritis **	43	13.4
Complete recovery (under age 30, in 90%) (over age 50, in <50%)	254	80.0

* Cases with scarlet fever, diphtheria or without history of acute infection excluded.

** 25 dead in 1½ to 18 years from onset. 18 living, 4 to 31 years of nephritis.

Rudebeck deliberately excluded cases without a history of acute infection at the onset of the nephritis in order to avoid the pitfall of latent or mild chronic nephritis. His material otherwise is similar to the accumulated data from other sources in that the preceding infection was upper respiratory in 88 per cent, erysipelas or pyoderma in 5 per cent, pneumonia and rheumatic fever in about 2 per cent each. He personally reexamined over half of the patients, carrying out Addis counts on the urine sediments of 75 per cent of this group. He found that if the urine was normal one year after the patient was asymptomatic, there was only a slight statistical chance of a return of abnormal findings; in the case of the blood pressure, a three year period of normality was conclusive. In the older age groups, a persistent hypertension in the absence of urinary changes made interpretation difficult, particularly when the blood pressure level prior to the acute nephritis was often unknown.

His report confirms the view that age is an important factor in the prognosis of acute nephritis. It agrees closely with data of Schwarz et al.,²³ on 244 children with acute nephritis—84 per cent recovery, 5 per cent death, 12 per cent chronic. It also seems to indicate that diet, level of blood pressure, amount of edema or albuminuria and even the early institution of bed rest are of little influence on the prognosis. However, the severity of the nephritis, as measured by degree of renal insufficiency, and its duration, are important in determining the tendency to chronicity. Severe oliguria or anuria and cardiac failure are of significance only in the immediate mortality

and not in the ultimate outcome of the disease. Rudebeck concludes that the course of acute nephritis is little affected by medical treatment, but probably determined by the original injury. Residual symptoms, so-called, must be taken seriously; they must have disappeared before the nephritis can be considered as healed. He considers the diagnosis of focal glomerulonephritis as dangerous, for the reasons I indicated earlier.

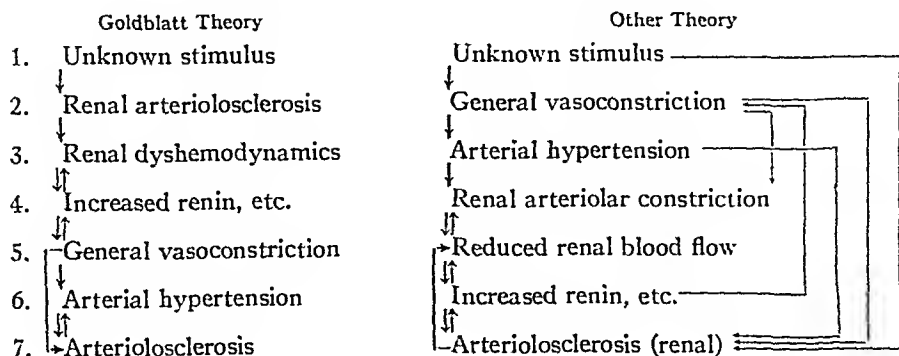
The remarkable absence of chronic nephritis after the acute nephritis complicating scarlet fever¹⁹ has never been adequately explained, although one is strongly tempted to attribute this result to keen medical and lay awareness of the possibility of acute nephritis; hence, early diagnosis and appropriate symptomatic treatment, of which bed rest is probably the most important. To what extent the immunological reaction to the streptococcal erythrogenic toxin contributes to renal recovery cannot be determined from the available knowledge of this process.

HYPERTENSIVE VASCULAR DISEASE

If we accept Goldblatt's²⁴ hypothesis that presenile renal arterio- and arteriosclerosis are the primary factors in "essential" hypertension, we have before us the most common and most important organic disease of the kidney—in fact, the most common and most important human organic disease. If, on the other hand, we agree with the large group of students of hypertension, who claim that the initiating factor of general vasoconstriction is unknown,^{25, 26, 27} perhaps psychogenic or neurogenic, and that the disturbance in renal hemodynamics is part of this functional vascular derangement, then we must consider high blood pressure as partly a manifestation of functional renal disease, ultimately ending in organic renal vascular disease through as yet unknown intermediate or parallel phenomena. The various alternatives are illustrated in table 4.

TABLE IV

Mechanism of "Essential" Hypertension



In favor of the functional theory are the perfectly symmetrical changes in glomerular and tubular function demonstrated in hypertensive patients by

Chasis and Redish,²⁸ the bilaterality of pathology or complete lack of it in renal biopsies on hypertensive patients shown by Castleman and Smithwick,²⁹ and the evidence for predominance of neurogenic factors early in human hypertension.³⁰ In the experimental Goldblatt animal, however, there is some evidence to the contrary—i.e., late central or neurogenic disturbance in blood pressure regulation with maintenance of an elevated pressure even after removal of the constricted kidney.³¹ Goldblatt³² does not accept these results for technical reasons and the matter is still sub-judice. It is to be hoped that the rapid development of pharmacologic hemodynamic tools in the form of the various adrenolytic, sympatholytic and autonomolytic drugs of the Fournieu or methylbenzodioxane³³ tetraethylammonium³⁴ or dibenamine³⁵ series will soon enable us to draw up a percentage composition table for hypertensive patients in which we could indicate what percentage of a given subject's mean blood pressure is due to ordinary sympathetic vasomotor tone; what percentage to momentary epinephrine or sympathin release due to excitement or exercise; what percentage to excessive continuous or paroxysmal release of epinephrine from an adrenal medullary tumor or other pheochromocytoma; what percentage to excessive renin or its products; what percentage to excessive delivery of salt-retaining and other vasopressor steroids from the adrenal cortex or elsewhere, and what residual percentage from organic narrowing of numerous small arteries and arterioles. Only by this complete pharmacologic analysis of arterial blood pressure shall we ultimately arrive at a satisfactory pathogenesis and, probably, rational therapeutics of hypertensive disease in man.

While awaiting this happy day with apneic respiration, it may not be amiss to point out the present confusion in the minds of many in regard to the harmfulness or harmlessness of hypertension per se; the arguments pro and con as to the relation between high blood pressure and general or renal arterio- and arteriolosclerosis—from which stems the important consideration as to the utility or futility of interrupting the sympathetic nervous pathways and, hopefully, lowering the blood pressure for a shorter or longer period. If, as Goldring and Chasis²⁶ say, the organic vascular disease proceeds more or less independently of the hypertension, are we not wasting the impatient energies of our surgical confreres? Perhaps—but we are learning some things about human neurovascular physiology.

Furthermore, many a general practitioner and many a young certified internist exclaim—"But what else can you do for the hypertensive patient?" They are, of course, too modest to estimate properly the great value of careful medical examinations of the psychosomatic type and the rôle of their own reassuring personality in maintaining a fair state of health for decades in many of their patients. They do not, like some surgeons, prophylactically exclude from their mortality and morbidity lists all patients over 50, over 45, over 40 or is it 35 years today; or all patients with established organic disease of the heart, retinal vessels, brain and kidneys; or patients with a host

of other items that bring the number admitted to candidacy for sympathectomy down to about 5 to 10 per cent of the average number seen and treated by the medical man. Speaking for medical treatment, perhaps we are not doing so badly as it sometimes seems.

However, we must face reality in this problem of hypertension and, therefore, turn all our energies in the direction of learning more about the mechanism of regulation of blood pressure in the normal and hypertensive states. A mass of evidence is accumulating from various directions that sodium retention in some manner is decisive in both experimental and human hypertension.^{36, 37} At least one of the effective means for lowering the blood pressure involves sodium depletion. The virtue of Kempner's³⁸ rice, fruit and fruit-juice diet undoubtedly resides chiefly in the low sodium content. The low protein and low fat intake, according to Grollman,³⁷ Dock³⁹ and some of our own observations, apparently have little to do with the therapeutic effect except that the protein of rice is exceptionally good cereal protein and well utilized. As a corollary of the studies on Addison's disease and the rôle of Doca (desoxycorticosterone acetate) in promoting retention of salt and water and causing or restoring hypertension if given in excessive doses, Perera⁴⁰ and his associates^{41, 42} have recently shown that patients with essential hypertension react to sodium restriction as though they had excessive Doca within them and that they develop rapid rises in blood pressure above their basic, control hypertensive figures when they are given Doca plus extra salt in amounts which in the normotensive subjects would require weeks to yield significant changes.

What this means in regard to the adrenal cortical rôle in hypertension and whether it supports Selye's³⁶ theory on the damaging renal, glomerular and vascular action of Doca plus salt, cannot be settled at present. But for those who believe in the psychogenic or neuro-endocrine theory of origin and perpetuation of hypertension, there are only a few feet of vascular and nervous tubing between the cortical-hypothalamico-pituitary axis and the adrenal cortex. Let us hope that it will not take too long to bridge the remaining gaps in our knowledge of the mechanism.

DIABETIC GLOMERULOSCLEROSIS

It is with deep humility, because of profound ignorance, that I approach this subject. Having had the somewhat frustrating experience of observing the late stages of 15 classical instances of this condition, with 11 autopsies, in the last five years at the Montefiore Hospital, I can only urge those of you who deal with diabetics in the first decade of their disease, to watch them as closely as possible for any clues as to the initiation of glomerulosclerosis. Two of our patients died in their late twenties. Dolger⁴³ has reviewed 25 years of experience with the management of 200 diabetics whose disease began before age 50. Among these were 55 juvenile diabetics, seven of

whom died, three with the Kimmelstiel-Wilson syndrome. The distressing feature is that regardless of the type of management employed, retinal hemorrhages developed in all his young patients within six to 22 years. Half of those with retinopathy had hypertension, and 30 per cent had albuminuria—in short, the makings of a diabetic glomerulosclerosis. You can appreciate the havoc caused by this disease when you learn that 14 per cent of Dolger's 200 diabetics were partially or totally blind, and that in some of our older patients impairment of vision was the first reason for seeking medical aid.

The diabetes may be so mild that a glucose tolerance test may be required for diagnosis. The blood pressure may not be elevated because of previous myocardial infarction. There may be no history nor presence of edema in rare instances of otherwise typical syndrome. The edema may be nephrotic in younger individuals with massive proteinuria and hypoalbuminemia and fair renal function. However, in patients over 55, proteinuria usually does not exceed 5 to 10 grams a day, the plasma albumin is often normal or only rarely below 3.5 grams per cent and the real reason for the patient's edema is congestive heart failure with elevated venous pressure and renal insufficiency, eventually progressing to full uremia.

Since all these patients show considerable renal arteriosclerosis and arteriolosclerosis at autopsy, it is not surprising that the specific nature of the syndrome was not fully appreciated until 10 years ago.⁴⁴ Given a patient over 50 with diabetes and retinopathy, one look at the urine sediment may be sufficient to make the diagnosis of diabetic glomerulosclerosis, if one finds some lipid or fatty cells or casts. A polarizing device is unnecessary for their recognition although it makes a pretty demonstration. Any good technician can be trained within a few days to spot the lipid cells or casts with the low power objective. In younger diabetics one has to consider chronic glomerulonephritis in the differential diagnosis. In some tuberculous diabetics, amyloidosis of the kidney may give rise to fatty cells and casts. The beauty of this simple method of diagnosis lies in the fact that hypertensive renal vascular disease, or nephrosclerosis, so commonly associated with diabetes in older individuals, does not produce a similar urinary sediment in this one respect. In fact, the finding of albuminuria and fatty cells by a reliable technician may furnish the first clue to the existence of diabetes in an older patient with congestive heart failure.

It is in the doctor's office and in the outpatient clinic for diabetes, that the beginning of this vascular complication or integral part of diabetes mellitus will have to be studied. Diabetic glomerulosclerosis is more important numerically than chronic glomerulonephritis, and there is every reason to believe that its incidence will continue to increase as its recognition spreads and as more diabetics live on for decades with their metabolic disease. We must vigorously attack the problems of the relation of the diabetes to the vascular disease—arterial, venous and capillary. The approach to this task is not simply one of this or that type of diet.

FUNCTIONAL RENAL DISEASES

In these days of increasing emphasis not only on the pathological physiology of disease but especially on the functional pathogenesis of the earliest stages of organic disease, one need make no apology nor give any argument for the inclusion of the great and important group of functional disturbances or diseases of the kidney in the classification (table 5). It is the growth

TABLE V
Classification

B. Functional Renal Diseases

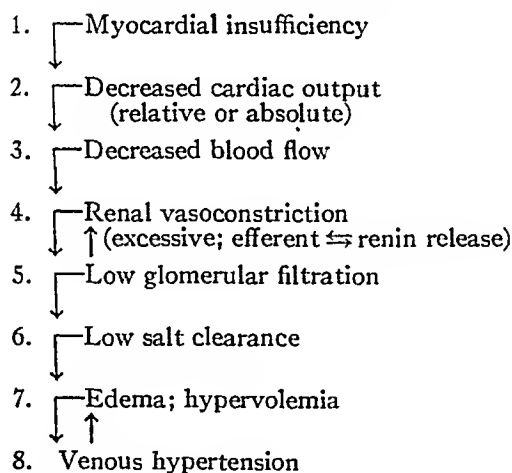
1. Vasoconstriction—
Hypertension
Cardiac failure
Albuminuria
Early shock
2. Tubulovascular—
Severe shock syndromes due to
Hemorrhage
Crush
Burns
Dehydration
3. Tubular—Hormonal—
Diabetes insipidus
Addison's disease
Cushing syndrome
Hypertension (?)
4. Tubular—Metabolic—
Renal diabetes
Fanconi syndrome
Other defects

of the tree of knowledge of renal hemodynamics, glomerular filtration, tubular reabsorption, tubular excretion and tubular metabolism so beautifully nurtured by renal physiologists in the last three decades, that is now yielding splendid fruit in applications to the clinical problems of shock, congestive heart failure, diabetes insipidus, adrenal cortical disease and hypertension, to mention only the most important.

It is nevertheless a remarkable fact that by stretching one's hemodynamic theories just a little here and there, it is possible to subsume the most important and most prevalent of human diseases, acute and chronic, under the heading of functional renal diseases. To take the chronic group first, a good case can be, and has been made out for essential hypertension as a disturbance in renal hemodynamics. I have already alluded to this in table 4. More recently, thanks to the work of Warren and Stead⁴⁵ and Merrill,⁴⁶ the edema of chronic congestive heart failure has been claimed to depend chiefly on reduced glomerular filtration, secondary to renal vasoconstriction, in turn presumably compensatory to reduced cardiac output, whether absolute or relative; in short, "forward failure" (table 6). If the kidney were not so generous in giving up a large part of its own huge blood

flow, for the benefit of more vital structures, cardiac patients would not develop edema so readily when their hearts fail. The real trouble, as my colleagues Mokotoff and Ross⁴⁷ have shown clearly, is that the renal tubule of the patient in congestive heart failure behaves exactly like a good normal tubule should—it reabsorbs the same amount of sodium (13.3 milli-equivalents per 100 c.c. of glomerular filtrate), as the tubule of a non-cardiac subject on a similar diet. Otherwise the serum sodium would not remain constant. Therefore, any reduction in glomerular filtration is immediately reflected in a much reduced clearance or excretion of sodium. If, in an edematous cardiac patient, the glomerular filtration rate is artificially increased toward normal by intravenous injection of aminophyllin, the excretion of sodium in the urine temporarily reaches the same rate as it would in the control subject with a similar glomerular filtration and serum sodium level, because the renal tubule keeps on reabsorbing the 13.3 milli-equivalents of sodium for every 100 c.c. filtrate, allowing the excess above this “threshold” to escape into the urine. When a mercurial diuretic is given, the filtra-

TABLE VI
Cardiac Renal Dysfunction



For “backward failure” read 1 → 8 →
 $\begin{array}{l} \rightarrow 7 \\ \rightarrow 5 \\ \rightarrow 3 \end{array}$

Exercise aggravates 4 → 5 → 6 → 7; 1 → 8 → 7

tion of sodium is unaffected but the tubule is slightly “poisoned” and falls below its usual reabsorptive capacity for sodium; hence a salt and water diuresis. You see, therefore, how easy it is to oversimplify the edema of congestive heart failure by blaming it on the blind performance of ancient homeostatic duties by perfectly normal renal tubules which, so to speak, cannot fish beyond the depth of their own glomerular filtrate and blood capillaries, nor ever cast their cytoplasmic rods into the distant water-logged tissue spaces.

Actually, there is a little more to cardiac edema than the function of the kidney as Landis⁴⁸ has shown, but this is not the time to discuss the other

aspects of the intriguing old problem except to reemphasize the practical implications as to control of salt in the diet of patients whose glomeruli cannot possibly filter out sufficient salt to exceed the reabsorptive capacity of their proximal and distal tubules. If you ask "Why not simply give a few more injections of a mercurial diuretic?"—the answer is: "Of course!", provided the patient's rate of reaccumulation of edema is reasonable. But when one, two or three injections a week are required to rid the body of 10 or 15 grams of salt and its associated water, is it not more sensible to reduce the dietary content of salt from 5 or 6 grams a day to 1 or 2 grams and slow down the rate of accumulation correspondingly? The virtues of adequate salt restriction have been rediscovered recently in various parts of the country from Montana⁴⁹ to Massachusetts⁵⁰ and, as more and more cardiac patients live on for years or decades with congestive failure, it will become more and more necessary to re-indoctrinate physicians, dietitians and patients in the details of low salt diets. Recent re-analysis of the sodium content of many natural and standard prepared foods by the rapid and precise flame photometer method,⁵¹ has furnished a somewhat more liberal basis for a palatable salt poor diet. The development of sodium-free, reconstituted milk has been helpful.⁵¹ The problem of a substitute for salt has not yet been solved, but it should not be insuperable in the near future if enough chemical and pharmacological aid is enlisted.

TUBULO-VASCULAR SYNDROME

Renal vasoconstriction, as already pointed out, is a rather general reaction occurring whenever the efficiency or integrity of the circulation is threatened by cardiac injury or disease, skeletal trauma, hemorrhage, dehydration, comas, etc. Presumably, the immediate effect of this diversion of blood from the kidney is to make more of the low cardiac output available to vital areas—heart, brain, lungs, liver. So far so good. A few hours of oliguria or even anuria is not a catastrophe; and it is a fact that the kidney can safely stand complete interruption of its arterial blood supply for 20 or 30 minutes. But when the state of renal vasoconstriction and marked ischemia persists for 12 to 24 hours or longer, something apparently happens to the vitality of the tubular epithelium and a whole series of dysfunctions arise, with or without structural alterations, that may lead irreversibly to uremia and death even though the original injury to the body or to the circulation may already have been corrected. This is well exemplified in the late renal deaths in the crush syndrome, after incompatible blood transfusion reactions, in post-operative reactions, in the so-called hepato-renal syndrome, various infections and intoxications, metabolic comas and other conditions too numerous to mention.

One may look upon this variety of conditions from a unitarian or multiple point of view. Furthermore one may consider them from the morphological or functional sides. Among the pathologists there has been a strong tendency recently to attribute much of the serious renal dysfunction to degen-

eration or obstruction of the distal convoluted tubules. Both Oliver⁵² and Lucké⁵³ have adduced striking histological and histochemical evidence for this concept. Lucké has used the term "lower nephron nephrosis" to designate this syndrome, which he considers the most frequent form of fatal renal disorder among military personnel. In civilian life, auto accidents and industrial, agricultural and mining injuries must furnish a large number of hitherto poorly recognized cases. It should be noted that the pathologist's emphasis on the distal convoluted tubule requires physiological confirmation and that it does not exclude dysfunction of the proximal convoluted tubule as the main disturbance.

Maegraith⁵⁴ in 1944 coined the term "tubulo-vascular syndrome" and reached the conclusion that only renal anoxia could fully account for the wide variety of clinical conditions associated with oliguria, anuria and uremia. Like some other investigators, he minimized the rôle of mechanical blockage of tubules by casts, débris, crystals, pigment or proteins and was unimpressed by the evidence for the nephrotoxic action of various hypothetical agents. While his unitary concept of renal anoxia is an attractive one in view of the high oxygen requirement of the kidney, it still lacks direct experimental proof, and may be too sweeping a generalization.

The dividing line between the tubulo-vascular functional disturbances and the organic chemical nephroses or necroses of tubules is a tenuous one, and, perhaps, of only temporal or quantitative significance in many instances. The important unifying feature is what McCance and Lawrence⁵⁵ have aptly called "functional disorganization" of the kidney. The renal tubule loses its highly selective ability to reabsorb certain elements and to discard other substances in the glomerular filtrate. Salt, non-protein nitrogen, glucose, water, acids, bases, etc., may diffuse back completely through the disorganized tubule especially since filtration is very low on the one hand, and on the other hand, there is often some blockage of distal and collecting tubules by casts, pigment, débris, sulfa and what not. Interstitial edema of the kidney, with a tense capsule, may add further to the functional confusion.⁵⁶ The net result is severe oliguria or anuria and uremic coma, superimposed on the patient's other troubles. The disturbance is often not recognized unless urine volume and concentration and the blood chemistry have been closely watched by the physician during his preoccupation with the patient's cardiac, peripheral vascular, pulmonary, cerebral or skeletal situation.

Time is of the essence if renal recovery is to result from treatment. There are only two alternatives—death from uremia or complete recovery. Chronic intermediate stages do not seem to occur. Furthermore, amazing blood chemical changes and dire general effects may be produced by indiscriminate infusion of this or that solution, due to slow response or lack of selective response by the kidneys. In severe instances in the past, after urinary tract obstruction was excluded by ureteral catheterization and the usual medical measures had failed, decapsulation had to be considered, often

too late. Today, the ingenious and well-tested artificial kidney of Koiff⁵⁷ should be a godsend for patients with previously good kidneys, because it is the ideal heroic treatment to tide the patient over the renal "blitz." Lacking this device, the alternative, although a rather poor one, is peritoneal irrigation for several days.⁵⁸ Even a brief experience with this method or any method for restoring renal function in this group of tubulo-vascular conditions, is sufficient to impress one with the profound wisdom and specific gravity of the old saying about the ounce of prevention. Therefore, the first line of attack in the treatment of medical or surgical shock, after pain, anoxia and hemorrhage have been counteracted, is meticulous provision of proper conditions and materials for kidney function, leaving nothing to guess work. The 24 hour urine volume, measured at each voiding or every six hours by catheter, may be far more important than the rectal temperature, or the pulse rate. Decisions as to need for parenteral fluids should be made several times, not merely once, in 24 hours.

The only safe diuretics in this condition of renal ischemia and tubular damage are a normal circulating and well-oxygenated blood volume, a balanced electrolyte and glucose solution preferably hypotonic as to salt, unless the serum values are quite low, with enough bicarbonate or lactate to counteract acidosis present or expected, and in the case of children with diarrheal states, with adequate potassium.⁵⁹ Mercurial diuretics are mentioned only because they should be strictly avoided. They have no place in the treatment of the tubulo-vascular syndrome. The plasma volume, hematocrit, plasma protein and serum sodium, chloride, CO₂ and potassium, as well as the blood urea or non-protein nitrogen, must be determined at appropriate intervals to aid in the intelligent use of the therapeutic procedures just outlined. Otherwise, one pours bottles into the circulation in the dark and enjoys or suffers the chance consequences.

Specific Tubular Dysfunctions. Just a few comments on the specific or isolated tubular dysfunctions associated with striking clinical syndromes, such as diabetes insipidus, Addison's disease of the adrenals, its opposite number the Cushing syndrome, renal diabetes, the Fanconi syndrome, and acidotic osteomalacia. It is evident that the first two diseases represent the effect of lack of hormones produced outside the kidney, but with the chief symptoms resulting directly from the renal functional disturbance. In other instances, like the Cushing syndrome, renal symptoms form only a small part of the clinical disease. In a third group, the tubular metabolic diseases, the primary defect is in the chemical organization of the tubular cytoplasm, presumably on a congenital basis. This is revealed in an isolated inability, of varying quantitative degree, to manufacture ammonia,⁶⁰ or to reabsorb amino-acids, phosphate or glucose adequately.⁶¹ A remarkable type of disturbance is seen in a small percentage of patients with advanced nephritis whose tubules fail to reabsorb sodium to a degree comparable with the situation in severe adrenal cortical insufficiency.^{62, 63} However, in the nephritic

cases, adrenal hormones are ineffective and the only effective treatment is a high intake of sodium chloride to compensate for the continued loss.

We shall learn much in the near future from modern renal physiological studies on patients with various tubular disturbances of hormonal or renal metabolic nature. The diagnosis of mild diabetes insipidus can be difficult but is readily made with the procedure of Hickey and Hare⁶⁴ in which the ability of the patient's hypothalamic-pituitary mechanism to respond to intravenous hypertonic salt solution is measured grossly by the effect on urine volume, and, in a more refined manner, by the change in concentration ratio of chloride in the tubular reabsorbate (R) to the chloride in the plasma (P). In the normal person, hypertonic salt solution (2.5 per cent) intravenously calls forth an increased secretion of pituitrin which sharply reduces the rate of urine flow and increases the chloride concentration in the urine because it increases the amount of water reabsorbed by the distal renal tubule. Hence the R/P ratio falls below one. In diabetes insipidus, the posterior pituitary cannot respond to hypertonic saline, the urine volume is not diminished, in fact increased by the extra salt, and the R/P ratio, which is above 1, does not change. This is a neat and objective test for the distinction of true diabetes insipidus from primary thirst and polydipsia.

For those who believe in the antagonism between pituitrin and adrenal cortical salt-retaining hormones as they act upon the renal tubule, opportunities to test the theory are afforded by unique clinical endocrine cases such as severe hypopituitarism, the Cushing syndrome and other conditions. Soffer's⁶⁵ salt and desoxycorticosterone test for adrenal cortical hyperfunction takes advantage of the altered renal response in a practical diagnostic test even though he has no adequate explanation for the results. We have already referred to the special behavior of the kidneys in essential hypertension toward sudden restriction of salt in the diet, or to the administration of Doca. These are only a few examples of the use of specific renal tubular functions in diagnosis and in the elucidation of pathological physiology.

Unfortunately, we still know next to nothing of the mechanism of renal diabetes or the other tubular metabolic or enzymatic disturbances of which the renin pressor and other vasoconstrictor activities⁶⁶ may be important consequences. However, the rapid progress of biochemistry of intermediary metabolism with the aid of isotopes should soon fill in many gaps in our knowledge of the kidney's tubular housekeeping, as it has done in the case of the liver.

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727 MENINGOCOCCIC CASES: AN ANALYSIS*

By ARCHIBALD L. HOYNE, M.D., F.A.C.P., and ROWINE HAYES BROWN, M.D., *Chicago, Illinois*

ALTHOUGH an unusual amount of material in regard to meningococcic meningitis has been published since the introduction of the sulfonamides, and especially more recently following the discovery of penicillin, we believe our experience during the past few years is of more than ordinary interest.

From January 1, 1943, to December 31, 1946, there were 727 patients admitted to Municipal Contagious Disease Hospital with a diagnosis of meningococcic meningitis. The presence of meningitis accompanying meningococcemia might be questioned in 218 instances because no lumbar puncture was made, but in reality the clinical diagnosis was evident with few exceptions. There were 47 in which meningococcic infection was not confirmed by laboratory findings. Most patients who had no lumbar puncture did have either a positive blood culture for meningococci or a positive petechial smear. Ninety-seven per cent of our patients were treated without resort to either intrathecal therapy or spinal taps for drainage. The success attained by this plan is additional proof^{1, 2, 3} that our method of therapy is justified.

March and April, as customary in this area, were the peak months of incidence; admissions for those months totalled 102 and 91 respectively for the four years (table 1). During the same period, September furnished the

TABLE I
Admission by Months

Month	1943	1944	1945	1946	Total
January	5	34	25	21	85
February	10	29	16	11	66
March	13	41	26	22	102
April	17	49	15	10	91
May	20	30	12	5	67
June	14	18	9	3	44
July	13	8	6	3	30
August	13	6	9	4	32
September	7	8	5	6	26
October	22	23	9	2	56
November	19	16	18	2	55
December	33	19	17	4	73
Total	186	281	167	93	727

smallest number of patients, which was only 26. Among all patients the ages ranged from seven weeks to 71 years. There were 39 infants less than a year of age, while on the other hand 127 patients were more than 35.

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From Municipal Contagious Disease Hospital, Chicago Health Department.

These age groups are of special importance because both are not usually included in reports coming either from children's hospitals or from military sources. Moreover, 315 or 43.3 per cent were females, a group not ordinarily found in the latter classification. Sex did not seem to be an important factor in respect to susceptibility at any age. In table 2 the cases are ar-

TABLE II
Patients According to Age and Sex

Year	0-1		1-5		6-10		11-25		26-35		36-45		46-65		66 plus		Total
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
1943	5	11	24	21	7	12	27	23	10	7	11	10	7	11	0	0	186
1944	8	6	52	26	15	14	51	30	21	13	10	9	7	16	2	1	281
1945	6	1	32	14	8	4	34	19	9	10	9	8	7	3	1	2	167
1946	1	1	20	14	5	6	12	14	3	4	4	1	3	4	1	0	93
Totals by Sex	20	19	128	75	35	36	124	86	43	34	34	28	24	34	4	3	727
Totals by Age	39		203		71		210		77		62		58		7		727

Total Males.....412

Total Females.....315

ranged according to age and sex. All but 82 were white. There were 74 Negroes, 5 Mexicans, 2 Japanese, and 1 Philippino.

The average day of illness at time of admission was 3.1. But as it became generally known that meningitis was prevalent, the diagnosis was made more promptly in the third and fourth years than it was in the first two. This seems apparent because in 1943 the average day of illness from the onset until hospitalization was 3.7 for 186 patients, whereas in 1945 the corresponding average was 2.9 for 167 patients, and in 1946 it was 2.6 for 93 patients.

White blood counts were rarely excessively high, but ranged above 50,000 per cu. mm. in a few instances. The average leukocyte count for all patients was 17,360 per cu. mm. Blood cultures were positive in 51.4 per cent of 400. Among the 727 patients petechiae were present in 62.8 per cent, and for the latter blood cultures were positive in 42.7 per cent. Meningococci were found in smears from petechiae in the skin or mucous membranes of 153 patients, or 69.8 per cent of those examined. Because lumbar punctures were usually made only for the purpose of establishing a laboratory diagnosis, 41.8 per cent of the patients had no intrathecal tap after coming under our care; 29.9 per cent of all patients had no intrathecal tap either before or after admission (table 3). The average number of lumbar punctures for the entire series was less than one. Among the 423 patients whose spinal fluid was examined, smear or culture was positive for meningococci in nearly every instance (94 per cent). Spinal fluid cell counts averaged 11,491 polymorphonuclears per cu. mm.

TABLE III

Patients Who Had No Intrathecal Taps Either Before or After Admission

Year	0-1		1-5		6-10		11-25		26-35		36-45		46-65		Total		Total	Positive	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F		Blood Culture	Petechial Smear
1943			4	4	1		5	3	1				2	1	13	8	21	6	1
1944			26	9	5	7	16	7	5	1	4	4	1	4	57	32	89	40	47
1945	3		19	9	3	3	13	10	1	2	2	1	3	1	44	26	70	40	44
1946			11	10	2	1	6	3		1		1	1	2	20	18	38	23	28
Total	3		60	32	11	11	40	23	7	4	6	6	7	8	134	84	218	109	120

Typing of the organism was done in 241 instances. Of these 224 or 92.9 per cent were Type I. Nine patients suffered from Type IIa, seven from Type II, and there was but a single example of Type Ia. Inasmuch as Type I commonly predominates during most outbreaks of epidemic meningitis these figures are not surprising. All 17 patients not infected with Type I recovered. In view of the paucity of types other than Type I, the value of typing was not of major importance.

Two hundred ninety-eight or 40.9 per cent of the patients were comatose at the time of admission, and 74 or 10.1 per cent had one or more convulsions after hospitalization. There were only 28 or 3.8 per cent who showed evidence of opisthotonus and in nearly every instance where this occurred, it was present when the patient entered the hospital. This low figure is in sharp contrast to the frequency of opisthotonus during the days of intrathecal treatment with serum.

Diagnosis. Our routine procedure for hospital admissions consisted of a complete physical examination which included a white blood count, red blood count, and drawing of blood for culture. These procedures were carried out for every patient suspected of having meningitis, regardless of any special evidence in respect to the causative organism. In most cases smears were made from petechiae if the latter were present. All these routine measures were performed in the examining room before the patient was assigned to an isolation room or hospital ward.

The manner in which the diagnosis was established has been referred to. Nevertheless, we believe it is interesting to mention some of the conditions we were called upon to differentiate in the examining room. Approximately 41 per cent of all patients diagnosed as "suspect meningitis" prior to admission were found to be suffering from other conditions which included the following: brain tumor or abscess, spinal cord tumor, subarachnoid hemorrhage, poliomyelitis, epilepsy, tetanus, delirium tremens, and hysteria. Some with respiratory conditions which had been erroneously diagnosed as meningitis actually had such infections as tonsillitis, pharyngitis, sinusitis, various types of pneumonia, and in two instances foreign bodies in the

bronchi. Others with pertussis, scarlet fever, or German measles were also thought to have meningitis before entering the hospital. On a few occasions gastrointestinal conditions had been confused. Children were sent to us with intussusception, intestinal obstruction, gastroenteritis, or dysentery. Cardiovascular diseases gave cause for meningitis to be suspected. Acute rheumatic fever, subacute bacterial endocarditis, and valvular heart disease were sources for confusion. Chronic diseases were a basis for error in some cases where the patient was actually in diabetic coma, had diabetes and bronchopneumonia, chronic nephritis or uremia. Even dermatological conditions led to mistakes in the original diagnosis because dermatitis medicamentosa, erythema multiforme bullosa, papulonecrotic tuberculides, urticaria, and minute points of telangiectasis had evidently been regarded as skin manifestations of epidemic meningitis. Two men with typhoid fever and three with malaria had also been considered as possible cases of meningitis and were sent to the hospital for that reason. On the other hand, a number of patients who were reported as poliomyelitis, Von Economo's encephalitis, measles or chickenpox, were found after hospitalization to be suffering from meningococcic infection.

Complications. Exclusive of reactions which may be attributed to drugs, 23.3 per cent of all patients suffered from complications. There were 170 such patients. Arthritis was observed most commonly and occurred in 70 instances or 9.6 per cent. Deafness and panophthalmitis, fairly frequent in the days of intrathecal treatment, were comparatively rare in our series. In eight cases deafness was complete, occasionally being noted early in the course of the illness, but more often late. However, the disclosure could not always be made at the time of admission because some patients were comatose on arrival. There were eight additional instances in which deafness was partial, and in all of them improvement in hearing was either observed or anticipated at a future time. On the other hand, our experience has been that when hearing is entirely lost it is seldom regained. Panophthalmitis occurred twice and was present in both patients at the time of hospitalization. Hydrocephalus was a rare complication, and its presence determined only twice. These patients were infants, one two months and the other three and one-half months; both had hydrocephalus to a marked degree when admitted. Twenty patients had pulmonary involvement and all but four of these had bronchopneumonia. Among the 20 there were 12 deaths. There were also 12 others with terminal bronchopneumonia which was disclosed at autopsy. An unusual complication with recovery was pericarditis and effusion, generally a fatal occurrence. Another complication was facial paralysis which was noted eight times. Although a paralysis of this nature in acute infectious disease patients is rather frequently associated with a suppurative otitis media, none of these eight patients showed evidence of ear involvement; therefore, the condition may be explained on the basis of a toxic neuritis. None of the eight patients recovered the full use of

their facial muscles while in the hospital. One patient had a flaccid paralysis of an arm, another had a wrist drop, and a third a hemiplegia. Strabismus was present in 13 instances and otitis media in 12. Four patients had diplopia, 11 had conjunctivitis, and six had endophthalmitis. In none of these with ocular involvement was there complete loss of vision.

Treatment—Sulfonamide. No criterion was adopted for the selection of a sulfonamide. But an effort was made to use a fair diversity of the several drugs among the patients. The number treated with sulfadiazine and sulfathiazole was almost exactly the same. The small group given sulfamerazine may be explained by the fact that this drug was not available at all times. And long before the period had elapsed during which our series was completed, it seemed apparent that sulfapyridine did not approach in efficiency the other drugs that were employed. Nevertheless, all four groups seem to provide some suitable figures for comparison.

Irrespective of the drug used, the general plan of dosage was the same. In nearly all cases the initial dose of the medicament was by vein, and thereafter the sulfonamide was given orally when possible. Only in comatose patients was the intravenous injection repeated. In a comparatively small number, sulfonamides were administered subcutaneously. In determining dosage the weight of the patient was not given primary consideration, as commonly advised, but rather the seriousness of the illness and its duration. The initial dose for adults generally varied from 5 to 7 grams, and thereafter from 2 to 1 gram at four hour periods for all drugs with the exception of sulfamerazine with which the intervals were from six to eight hours. The average initial dose for children irrespective of age ranged from 3 to 5 grams which was followed by 1 gram every four hours. However, for infants the maximum initial dose rarely exceeded 2 grams which was nevertheless followed by 1 gram doses at four hour intervals. The average initial dose for all patients in our series, regardless of the drug, was 3.8 grams. The average varied from 4.1 grams for 186 patients treated in 1943 to 3.5 grams for 167 treated in 1945. For intravenous injection a 5 per cent solution of the sodium salt of the drug in normal saline was given, but for subcutaneous treatment the same preparation was employed in a 2.5 per cent solution.

The total average amounts of the drug per patient were: sulfadiazine 41.2 grams; sulfathiazole, 41.4; sulfapyridine, 41.0, and sulfamerazine 29.2 grams. Because there is such a sharp difference between the average amounts of sulfamerazine and the other drugs we believe that the larger doses used for sulfadiazine, sulfathiazole, and sulfapyridine are not essential for successful treatment. Although an effort was made to provide an adequate amount of fluids for each patient, the same degree of importance was not attached to administration of alkalies as a requirement. The average amount of parenteral fluid during the period of sulfonamide therapy was 3,728 c.c., and were it not for the fact that an abundant amount of fluids was given orally, the fluid intake for patients would appear to be low. We

usually prescribed from 2,000 to 3,000 c.c. of fluid for each 24 hour period with the exception of infants where the quantity was reduced in proportion to their size. One or more of the following fluids was customarily given parenterally: 5 or 10 per cent glucose in either saline or distilled water, 5 per cent glucose in Ringer's, Hartman's solution or M/6 sodium lactate.

Sulfonamide Blood Levels. Mention has been made that regardless of the drug selected there was practically no variation in dosage. Consequently, it has seemed particularly interesting to note the average levels for the different drugs. In every case a blood level was determined the day after patient's admission, and therefore the first blood level was secured within 12 to 24 hours following the initial dose of the drug. As a rule, several additional blood levels were obtained. The number of samples of blood for this purpose was based upon the response or lack of response to treatment or because of some drug reaction.

TABLE IV
Blood Levels and Fatality Rates According to Drug

Sulfonamide	Cases	Primary Blood Level	Average Blood Level	Deaths	Fatality Per Cent
Sulfadiazine	264	20.7	18.9	37	14.0
Sulfathiazole	263	7.7	7.1	34	12.8
Sulfamerazine	127	16.4	14.7	17	13.3
Sulfapyridine	68	13.9	10.7	17	25.0

In table 4 the primary levels for the various drugs and the average of all levels for each drug are shown. It appears that the highest blood levels after the initial dose, 20.7 mg. per cent, were obtained with sulfadiazine. Moreover, when the average of all levels was computed it was found that sulfadiazine with 18.9 mg. per cent was considerably higher than any of the corresponding levels for the other drugs which were: 14.7 for sulfamerazine, 10.7 for sulfapyridine, and 7.1 for sulfathiazole. It is especially noteworthy that both the primary and also the averages of all levels were lowest with sulfathiazole. However, with sulfathiazole the figures for the primary levels and the average level showed a smaller degree of difference than occurred between the primary levels for any of the other drugs.

Based on the figures presented in table 4 it seems proper to infer that the importance attached to sulfonamide blood levels has been overemphasized. It also seems likely that in the case of the drugs used dosages were much higher than may be required for satisfactory treatment. The first statement in this paragraph is really more than an inference because the fatality rates in our series for sulfadiazine, sulfamerazine, and sulfathiazole were practically the same (table 4). This was true, notwithstanding that the average of all blood levels for sulfadiazine was more than two and one-half times the corresponding average for sulfathiazole. And the average of all blood levels for sulfamerazine was more than twice the corresponding average for sulfa-

thiazole. Our figures suggest that high blood levels may not be an essential requirement for the efficient treatment of meningococcic meningitis. Furthermore, since low blood levels mean still lower spinal fluid levels, it seems apparent that the amount of the drug which enters the cerebrospinal fluid circulation is not necessarily a determining factor in the recovery of the patient.

Average Number of Days on the Sulfonamides. Although there was no prearranged plan in regard to any definite number of days for therapy, we find, irrespective of the sulfonamide employed, that the average length of time in 1943 and 1944 was almost identical; the figures were 8.7 and 8.9 days. But in 1945 many patients received the drug for a shorter period and the average time was 7.5; this was reduced still further to only 6.7 days for the year 1946. As a consequence the average duration of sulfonamide medication for our entire series was 8.3 days, but we found that in many instances five days' treatment was sufficient. All of these averages refer to recovered patients.

From the standpoint of economy of time on the part of patients and also the availability of beds and cost of care, the period of hospitalization deserves important consideration. Notwithstanding that we have been overcautious in regard to releasing patients until we felt that they had completely recovered from their illness, the average duration of hospitalization for all recovered patients was only 11.5 days. For the 150 recoveries in 1943 the average lapse between admission and discharge was 13.3 days, whereas in 1946 the corresponding average was reduced to 9.8 days. These figures are scarcely more than half as great as some that have been published.⁴ Moreover, they are in sharp contrast to the time when intrathecal serum was in vogue and three to five weeks' hospitalization⁵ was not unusual. The minimum isolation period for meningococcic meningitis in Illinois is one week from the date of onset.

TABLE V
Hematuria with Different Drugs

Drug	Cases	Hematuria	Per Cent
Sulfadiazine	264	154	58.3
Sulfapyridine	68	28	41.1
Sulfamerazine	127	44	34.6
Sulfathiazole	263	53	20.1
Total	722	279	38.6

Complications Associated with Sulfonamide Treatment. In table 5 drugs are indicated together with the number of patients who developed hematuria including microscopic as well as gross blood. The percentage of those who had hematuria with the different drugs is also shown. It may be seen that sulfadiazine was chiefly responsible for this condition. Moreover,

it is strikingly apparent that sulfathiazole was less often the offender than any of the others. The high percentage (58.3) for hematuria with sulfadiazine follows closely our past experience.⁶ In addition the low figure (20.1 per cent) for patients treated with sulfathiazole is also in conformity with former observations.⁶ There was a single fatality resulting from anuria and this occurred in the sulfadiazine group. We implied previously that the value of giving an alkali when using sulfonamide drugs is probably not of as great importance as the administration of adequate amounts of fluid. Our basis for this view is that 58.2 per cent of the patients received alkali, usually soda bicarbonate, in doses equal to or more than the amount of drug administered, and yet there was no significant difference in hematuria frequency for the group that had an alkali and the group that did not.

Herpes simplex occurred in approximately 8 per cent of our patients. However, in nearly all cases it did not develop until after several days' administration of sulfonamides and therefore was attributed to a drug reaction in most cases. Maculo-papular eruptions associated with conjunctivitis were noted in a few instances, the most severe ones being in the sulfamerazine treated group. Several patients had an erythema nodosum during sulfathiazole or sulfadiazine therapy. In infants and small children a hyperpyrexia was occasionally observed late in the course of sulfonamide administration and subsided upon cessation of the drug. Unless reactions were of unusual severity or manifest late in the course of treatment, sulfonamide therapy was not discontinued. Sometimes sulfanilamide was substituted when hematuria was present.

Penicillin Therapy. Among 727 patients there were 103 or a little more than 14 per cent who were treated with penicillin as well as one of the sulfonamides. Two patients received penicillin exclusively. In this group of 103 there were 27 deaths or a fatality rate of 26.2 per cent, indicating a death rate for the penicillin treated patients which was nearly three times greater than for those who received no penicillin. Among the 27 penicillin fatalities, nine received the drug intrathecally and two intravenously as well. Of the two patients given penicillin exclusively, one was treated by the intramuscular route and recovered, and the other received the drug entirely by vein and died. Both of these cases were meningococcemias rather than meningitis. Table 6 shows the number of patients who were given penicillin and a sulfonamide in combination and the outcome.

Our experience with penicillin for meningococcic infections has been disappointing. Because of the poor results secured with intrathecal administration⁷ this route was soon abandoned. Furthermore, we observed instances where as much as 600,000 units were injected intravenously within the first 24 hours of illness without any apparent effectiveness. In some cases penicillin was given alone at the customary three hour intervals in from 15,000 to 40,000 unit doses over a period of from five to six days without clinical improvement in the patient's condition. We were not convinced

TABLE VI
103 Patients Treated with Both Penicillin and Sulfa Drug

Year		0-1		1-5		6-10		11-25		26-35		36-45		46-65		Recoveries		Deaths	
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1944	Rec.			1	2				1	2	2					3	5		
	Died		1					1		3				1				4	2
1945	Rec.	4		8	5	3	2	4	5	3	3	1	3	2		25	18		
	Died	2		3	1			2		1	1	2		2				12	2
1946	Rec.			4	7	1	3	2	3		2	2		1		9	16		
	Died			2				3				1		1				7	
---	Total	6	1	18	15	4	5	12	9	9	8	6	3	6	1	37	39	23	4

that patients treated with both a sulfonamide and penicillin responded more rapidly than patients treated only with a sulfonamide. Notwithstanding our unfavorable views in regard to the value of penicillin for the general treatment of meningococcic meningitis, we believed that it was strikingly helpful for eye⁸ complications, but the opportunities for estimating its worth in such conditions were limited.

General Treatment. Regardless of the severity of the infection, we did not use either anti-bacterial serum or antitoxin.⁹ But for patients who showed evidence of shock or presented the customary picture of the Waterhouse-Friderichsen syndrome, adrenal cortical extract was injected. Generally the intramuscular route was adopted but we believe that some patients would have benefited to a greater degree if the intravenous route had been selected.¹⁰

The need for administration of sedatives, particularly morphine, in connection with the treatment of meningitis is often considered. In most of our cases no sedatives were prescribed. However, when patients were irrational one of the following drugs was sometimes used: phenobarbital, sodium amytal, seconal chloral hydrate, sodium bromide, or paraldehyde. For those who were very difficult to control we found paraldehyde to be of particular value. Contrary to the opinion sometimes expressed, we believe that morphine should not be used for meningitis. Our opposition to the last named drug is based on personal observations. There seems to be no doubt that morphine may produce or increase edema of the brain as well as depress the respiratory center. Progress toward recovery appeared to be retarded in those patients who received morphine prior to hospitalization. In every case bed restraints should always be applied during the acute stage of the disease.

Prognosis and Fatality Rates. Age is always considered one of the im-

portant factors in prognosis and this is shown to be true in our series, for those in the two extremes of life suffered the greatest casualties. Prognosis was most favorable in the groups from six to 10 years of age and among those from 11 to 25 as exhibited in table 7.

TABLE VII
Fatality Rates by Age

Age	Cases	Deaths			Fatality Per Cent
		24 hour	48 hour	Total	
0-1	39	5	2	11	35.4
1-5	203	18	4	24	11.7
6-10	71	2	0	2	2.8
11-25	210	8	4	19	9.0
26-35	77	2	4	11	14.2
36-45	62	4	3	16	24.5
46-65	58	7	2	21	36.2
65+	7	1	1	4	57.1
Total	727	47	20	108	14.8

Excluding 24 hour deaths—Fatality rate 8.9 per cent.

Excluding 48 hour deaths—Fatality rate 6.2 per cent.

Race seemed to play an insignificant part in prognosis. There were 645 white patients with a fatality rate of 14.8 per cent. Among 74 Negroes there were 10 deaths, or 13.5 per cent. There were also five Mexicans with one death, two Japanese who recovered, and one Philippino who failed to survive. Irrespective of race, the attack rate was higher for the males. Fifty-six and eight tenths per cent of the white patients were males, and 43.1 per cent were females. For Negroes 58.1 per cent were males and 41.8 per cent females. However, in both races the chances for recovery were slightly in favor of females, the fatality figures being as follows: white males 15.2 per cent; white females 14.3 per cent; Negro males 13.9 per cent; Negro females 12.9 per cent.

Patients entering the hospital in coma or suffering from convulsions were usually regarded as having a doubtful prognosis. This observation is not an uncommon one. Those with high temperature at the onset often responded better to sulfonamide therapy than the ones who had little fever. Possibly a marked pyrexia indicated to some extent the patient's degree of resistance.

Among all 727 patients there were 108 deaths or a fatality rate of 14.8 per cent. However, 67 died within 48 hours of admission, and included in the latter group were 47 where death occurred within less than 24 hours from the time of hospitalization. If these 47 were excluded the corrected fatality rate for 680 patients would be 8.9 per cent. With deduction of the 48 hour deaths which included all moribund cases, the fatality rate for 660 patients is 6.2 per cent.

Seventy-seven autopsies were performed and among these lobar or bronchopneumonia was present in 22 instances, as well as the customary intracranial findings. In 11 cases the Waterhouse-Friderichsen syndrome was confirmed at necropsy. As may be noted in table 4, the percentage of fatalities did not vary significantly regardless of the sulfonamide that had been used for treatment.

We were impressed by the fact that on a number of occasions in which the clinical diagnosis was strongly indicative of Waterhouse-Friderichsen syndrome, autopsy disclosed no gross or microscopic pathological changes in the adrenal glands. This may explain some of the reported recoveries in which the Waterhouse-Friderichsen syndrome was diagnosed.

SUMMARY

Among 727 meningococcic patients ranging in age from seven weeks to 71 years, there were 108 deaths, or a fatality rate of 14.8 per cent. Sixty-seven of the patients were moribund when admitted, and among these there was pathological or clinical evidence of the Waterhouse-Friderichsen syndrome in 20 instances. If all moribund patients are excluded, the fatality rate is 6.2 per cent.

A large number of the patients had meningococcemia and nearly all showed evidence of meningitis; 62.8 per cent had petechiae, and 69.8 per cent of the petechial smears were positive for meningococci. Fifty-one and four tenths per cent of blood cultures were also positive for meningococci. Among the 423 patients who had an intrathecal tap as a diagnostic measure, the spinal fluid smear or culture was positive for meningococci in 94 per cent. There were 47 patients in whom an absolute diagnosis was not confirmed by laboratory procedures, although clinically most of these were examples of meningococcemia and some had received treatment before hospitalization.

When the clinical diagnosis was confirmed by petechial smear or positive blood culture an intrathecal tap was not considered necessary; as a consequence, the entire group of 727 patients had an average of less (0.7) than one lumbar puncture; 41.8 per cent of the patients had no lumbar puncture after admission. There were 218 or 29.9 per cent who had no spinal tap either before or after hospitalization.

Only 22 patients received intrathecal therapy, the remedy used being penicillin, and the fatality rate for this group was 40.9 per cent. They also received a sulfonamide.

There was but slight difference in therapeutic efficiency regardless of the sulfonamide drug that was administered. However, the actual percentage of recoveries was highest for the patients who were treated with sulfathiazole. Fatality rates for the several drugs were as follows (table 4): sulfadiazine 14 per cent; sulfathiazole 12.8 per cent; sulfamerazine 13.3 per cent, and sulfapyridine 25 per cent.

The average number of days ill prior to admission was 3.1 and the average number of days on sulfonamide therapy was 8.3. The length of stay in hospital for recovered patients averaged 11.5 days. In spite of the short period of hospitalization there was not a single instance of a relapse or recurrence¹¹ following release from isolation.

COMMENT

We feel that our results in the treatment of 727 patients with meningococcic infections are a conclusive demonstration that intrathecal therapy is not necessary for meningitis. Moreover, we have also shown that frequent lumbar punctures for drainage are not required. In our opinion, penicillin is not a valuable adjunct in the treatment of meningococcic infections but is an efficient aid in the management of eye complications. We have shown also that the sulfonamide blood level is not always a reliable guide for determining the effectiveness of the drug. Although sulfathiazole levels are low, there is no doubt in regard to this drug's usefulness¹² for the treatment of meningococcic meningitis. Therefore we question the emphasis which is customarily placed on the value of blood levels when considering prognosis.

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SPECULATIONS AS TO THE THERAPEUTIC SIGNIFICANCE OF THE PENICILLIN BLOOD LEVEL *

By HARRY EAGLE, *Baltimore, Maryland*

I. THE DIRECT BACTERICIDAL ACTION OF PENICILLIN

PENICILLIN is actively bactericidal in vitro ^{1, 2, 3, 4, 5, 6, 7}; and although the body's cellular or humoral defense mechanisms probably play a contributory rôle in vivo, that direct bactericidal action may be largely responsible for the therapeutic activity of the drug.

The susceptibility of a given organism to penicillin may be defined in terms of three concentrations (figures 1 and 2; cf. also ^{2, 6, 7}). The first is that which suffices only to reduce the normal rate of multiplication, and is illustrated by curve 0.004 in figure 1 and point A in figure 2. At a somewhat higher concentration (e.g. curves 0.006 and 0.008 in that figure and point B in figure 2), the organisms are killed faster than they multiply, so that there is a progressive, slow decrease in the number of viable organisms.† This minimally effective level approximates the "sensitivity" of the organism to penicillin as ordinarily defined, i.e., the concentration at which the organism fails to grow out visibly in culture. It does not, however, represent the most effective concentration of the drug. Even a slight increase in penicillin beyond this minimally effective level causes a striking increase in the rate at which the organisms are killed by penicillin. One soon, however, attains a concentration of penicillin at which the organisms are killed at a maximal rate (point C in figure 2, and curve 0.064 in figure 1). This maximally effective level of penicillin usually varies between two and 10 times the concentration which barely suffices to reduce the number of viable organisms (table 1); and even a 10,000-fold increase beyond this optimal level does not further increase the rate at which the organisms can be killed by penicillin.

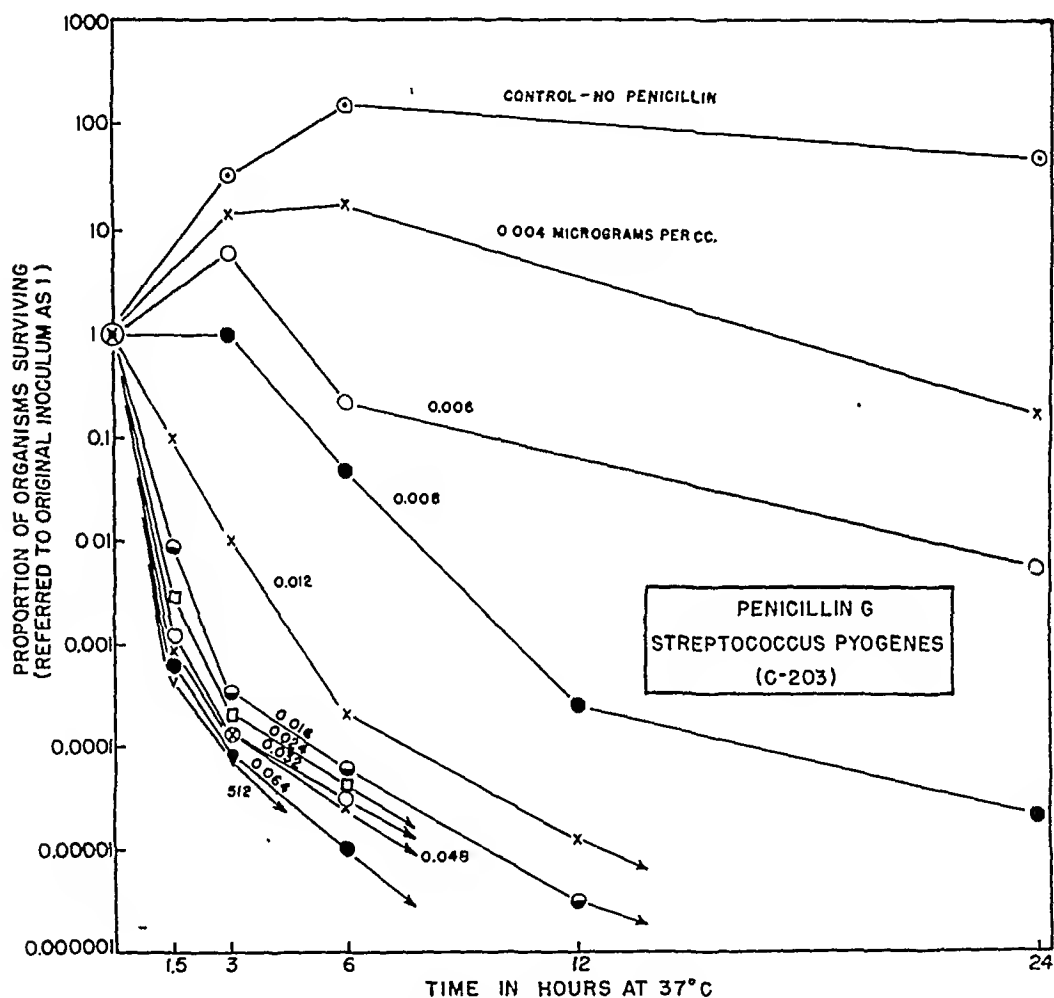
It is a reasonable surmise that the concentration of penicillin which is maximally effective in vitro indicates the approximate level which should be maintained at the focus of infection in vivo in order to kill the largest number of organisms in the shortest possible time. Coupled with information as to the distribution of penicillin between the blood and tissues, it may then be possible to use the penicillin plasma level as a guide to the most ef-

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From the Laboratory of Experimental Therapeutics of the U. S. Public Health Service and The Johns Hopkins School of Hygiene and Public Health, Baltimore 5, Maryland.

† With some organisms, at threshold concentrations of penicillin one often observes an initial net bactericidal effect, followed in six, 12, 24 or even 48 hours by their rapid multiplication, often to a degree exceeding that in a control culture. This secondary growth is not primarily due to the deterioration of penicillin, and will be discussed more fully in a following paper.

fective therapeutic use of penicillin. If the penicillin concentration is less than optimal during a large portion of the treatment period, then the time necessary to effect cure may be unnecessarily prolonged. On the other hand, excessively high concentrations serve no useful purpose as such, unless they can be shown to promote the body's own defense processes. The sole advantage of extremely large doses of penicillin may consist in the fact that



II. PHARMACOLOGIC CONSIDERATIONS

A. *The Penicillin Concentration in the Blood, and the Error in Its Bioassay Caused by the Presence of Serum.*

At a given moment, the plasma level of penicillin is being modified by many different factors.

(1) *Absorption from the site of injection.* When penicillin is injected intramuscularly in aqueous solution, by far the largest part of the injected

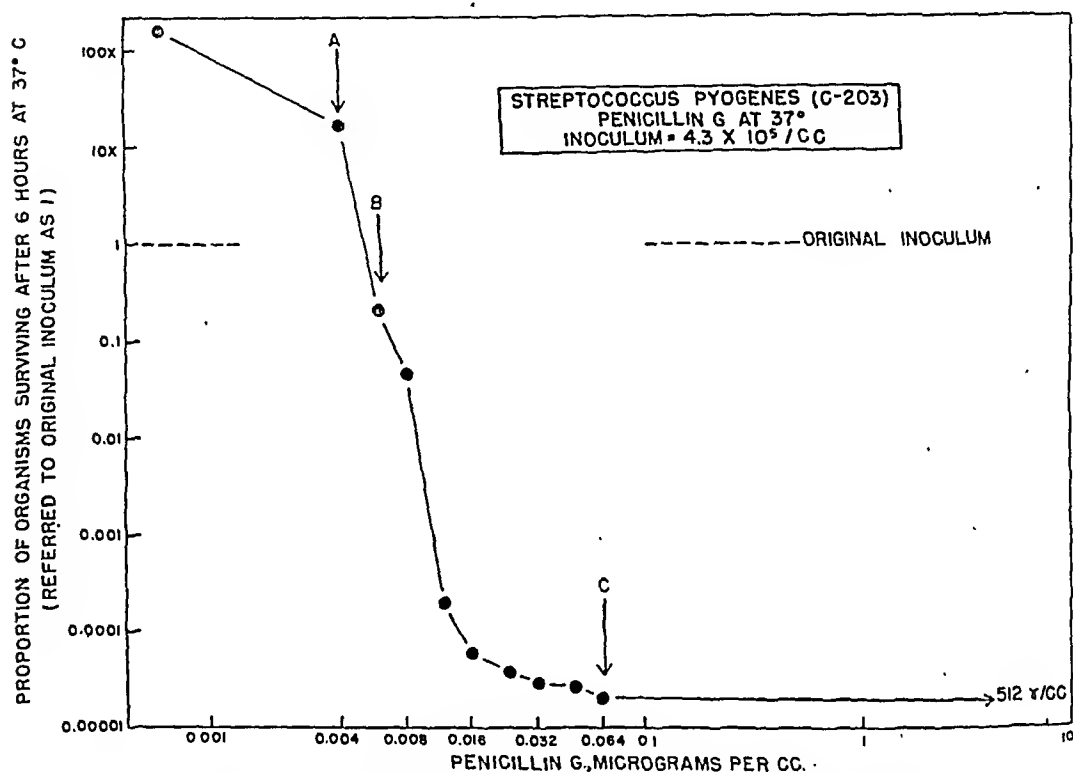


FIG. 2. The effect of the concentration of penicillin on the proportion of organisms surviving after 6 hours at 37° C. (from Eagle and Musselman²⁸).

penicillin has been absorbed in 15 minutes, so that the peak concentration is usually obtained in less than that time period, and is roughly proportional to the amount injected (figure 3, from⁹). Absorption is, however, markedly delayed by injecting a suspension of penicillin in oil and beeswax.¹⁰

(2) *Rate of urinary excretion.* Amorphous penicillin, and crystalline penicillins F, G, and X, are excreted by the kidney at a rate which corresponds essentially to the total removal of penicillin from all the blood reaching that organ.¹¹ (The anomalous low renal clearance of penicillin K is a special case which is not relevant to the present discussion.) It is primarily in consequence of this rapid excretion that the blood levels of penicillin fall so rapidly after a single intramuscular injection of an aqueous solution (figure 3).

TABLE I

"Effective Levels", of Penicillin G for a Number of Bacteria (Eagle and Musselman²⁸)

Infecting organism	Concentration of penicillin G (micrograms per c.c.) ^a which sufficed to			Time required to kill 99.9 per cent of organisms at optimal concentrations of penicillin	Proportion of organisms surviving after 6 hours exposure to maximally effective concentrations of penicillin
	reduce rate of growth	slowly kill the organisms	kill the organisms at maximum rate		
<i>Streptococcus pyogenes</i> (C-203)	0.004	0.006-0.008	0.064	1.5-2 hrs.	0.002-0.004%
Pneumococci (Types 1, 3, 8, 12, 14, 24)	0.008-0.012	0.024	0.064	3-5 hrs.	0.03%±
<i>Staphylococcus aureus</i> (6 susceptible strains) (1 resistant strain)	0.016-0.024	0.024-0.064	0.064-0.25	5-20 hrs.	0.05-1.0%
	0.25	1	16	11 hrs.	6%
<i>Treponema pallidum</i> (Reiter)	0.016	0.032	1±	25-35 hrs.	5-10%
<i>Streptococcus fecalis</i> (5 susceptible strains) (2 resistant strains) ^b	1	2-4	4-6	5 hrs.	0.05%
	1	3-4	4-6	>48 hrs.	10-50%

^a To transform to units, multiply by factor 1.7 (1 mg. = 1667 units).^b Resistant in that organisms were killed only slowly even at optimal concentrations of penicillin.

(3) *The inactivation of penicillins by plasma.* Penicillins F, G, and X have been shown to be slowly inactivated in plasma at 37° C. However, that inactivation proceeds so slowly as to be of negligible quantitative significance in comparison to the rate of renal excretion.

(4) *Diffusion of penicillin out of the blood into the tissues* continues as long as the concentration of diffusible penicillin in the plasma exceeds that in the tissues.

(5) *Diffusion of penicillin out of the tissues into the blood* begins as soon as the concentration of diffusible penicillin in the plasma falls below that in the particular tissue. Large injections may create a significant reservoir of penicillin in the body fluids and perhaps in the body cells; and the fact that, as is evident after large injections, the average plasma levels of penicillin fall off at a progressively slower rate may reflect the diffusion of penicillin back from this tissue reservoir into the blood (figure 3) (cf.^{20, 30}).

(6) *The effect of serum on the bioassay of penicillin.* In the determination of the penicillin concentration in the serum or other body fluids, the measuring rod ordinarily used is the inhibitory effect of the specimen on the growth of a susceptible test organism. A significant error may be intro-

tribution to the tissues at any moment is therefore only half the total plasma concentration. Finally, the magnitude of the concentration differential between the plasma and a given tissue will be materially affected by the rate at which penicillin is locally inactivated by that particular tissue.^{23, 24, 25} Although there are as yet no supporting experimental data, it is possible that penicillin may be not only inactivated, but also reversibly bound by the tissues. Under such circumstances the slow dissociation of penicillin from its com-

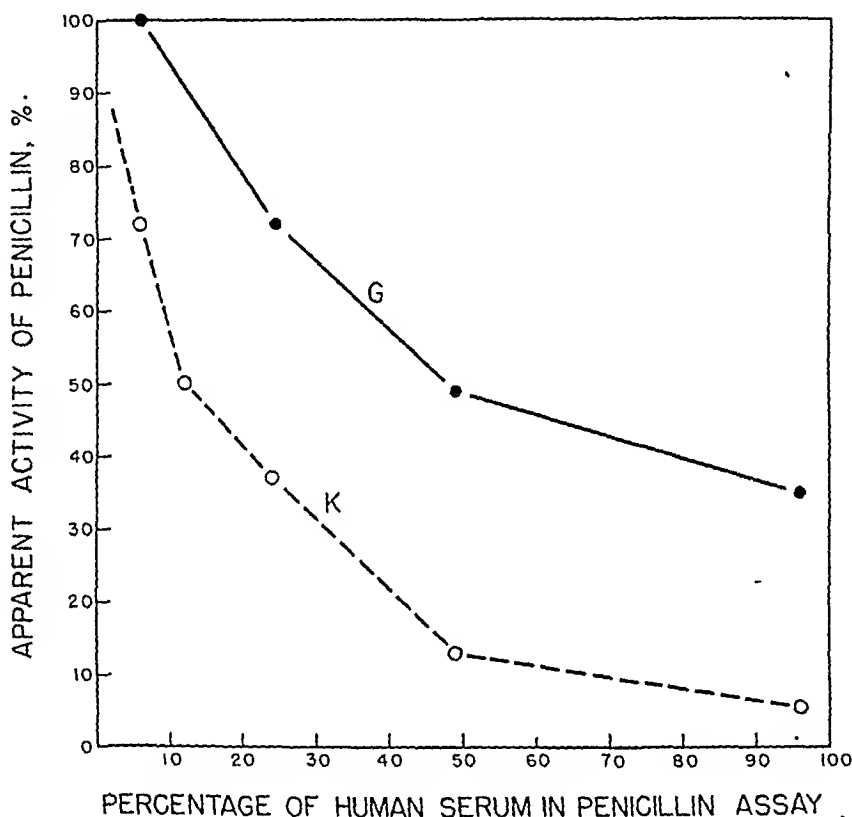


FIG. 4. The inhibitory effect of human serum on the bioassay of penicillin, with C-203 *Streptococcus pyogenes* as the test organism (from Eagle and Tucker³⁷).

Each point in the figure is the average of 8 to 11 determinations with as many different sera, as indicated in table 2.

bination with the tissues after it had largely disappeared from the blood might make it active locally for a much longer period than would be implied by the blood level curves.^{26, 30, 35, 38}

III. DURATION OF THE THERAPEUTIC EFFECT OF A PENICILLIN INJECTION^{26, 31, 35, 38}

The tissue penicillin levels after the intramuscular injection of penicillin in aqueous solution, and the therapeutic (bactericidal) activity of those levels, may be indicated diagrammatically as in figure 6. If concentration level A in that figure is that which kills a given organism at the maximal possible

rate, and B is the lowest concentration which, although not maximally effective, nevertheless does have a net bactericidal action in vitro, then the therapeutic efficacy of the injection may be measured in terms of three time periods, as indicated by the horizontal line at the bottom of that figure:

(1) The time for which the injection provides concentrations at the focus of infection equal to, or in excess of,* the maximally effective level A, and during which the organisms are being killed at the fastest possible rate.

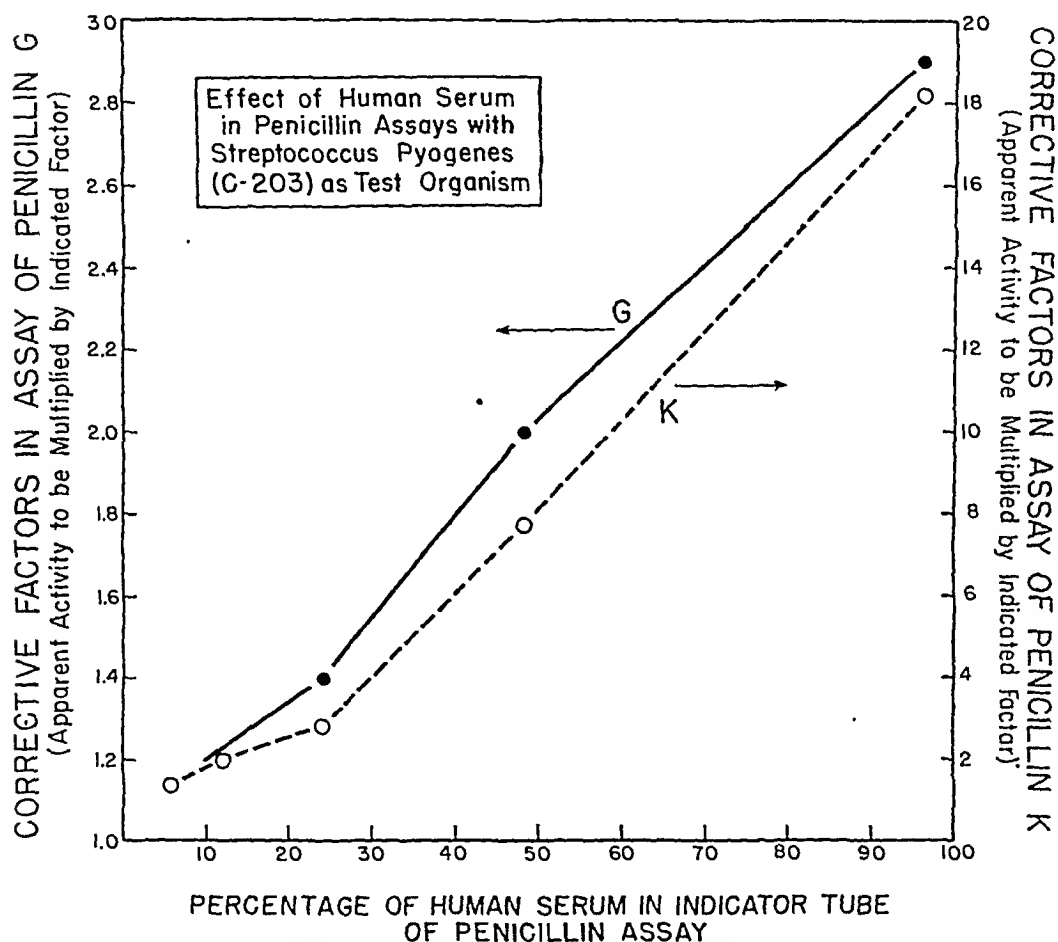


FIG. 5. Corrective factors in the bioassay of penicillins G and K (after table 2) (from Eagle and Tucker³⁷).

Abscissae are the concentrations of serum in the dilution which just suffices to inhibit hemolysis, and thus serves as the indicator of its penicillin content. Ordinates are the corrective factors by which that apparent penicillin activity must be multiplied in order to correct for the inhibitory effect of that concentration of serum on penicillin activity.

(2) The time for which the penicillin concentration is at effectively bactericidal concentrations, intermediate between the maximally effective level A and the minimally effective level B.

* This will not be true for organisms with a sharply defined optimal zone of penicillin concentration. For such bacteria, concentrations in excess of A are paradoxically less effective, and the time for which the concentration is in excess of that value is not a measure of the total therapeutic effect.

(3) Recovery period. Parker ³² has shown that when organisms are exposed to penicillin *in vitro*, the survivors do not begin to multiply as soon as the drug is removed. Instead, there is a definite recovery period before the surviving organisms begin to multiply to a significant degree. *In vivo* also, the experiments of Jawetz ²⁶ indicate that in infected mice treated with penicillin, the number of surviving viable bacteria continues to fall for some time after the serum penicillin has fallen to concentrations far below those which are effective *in vitro*. Whether this continuing disappearance of bacteria reflects the persistence of penicillin in the tissues for some time after

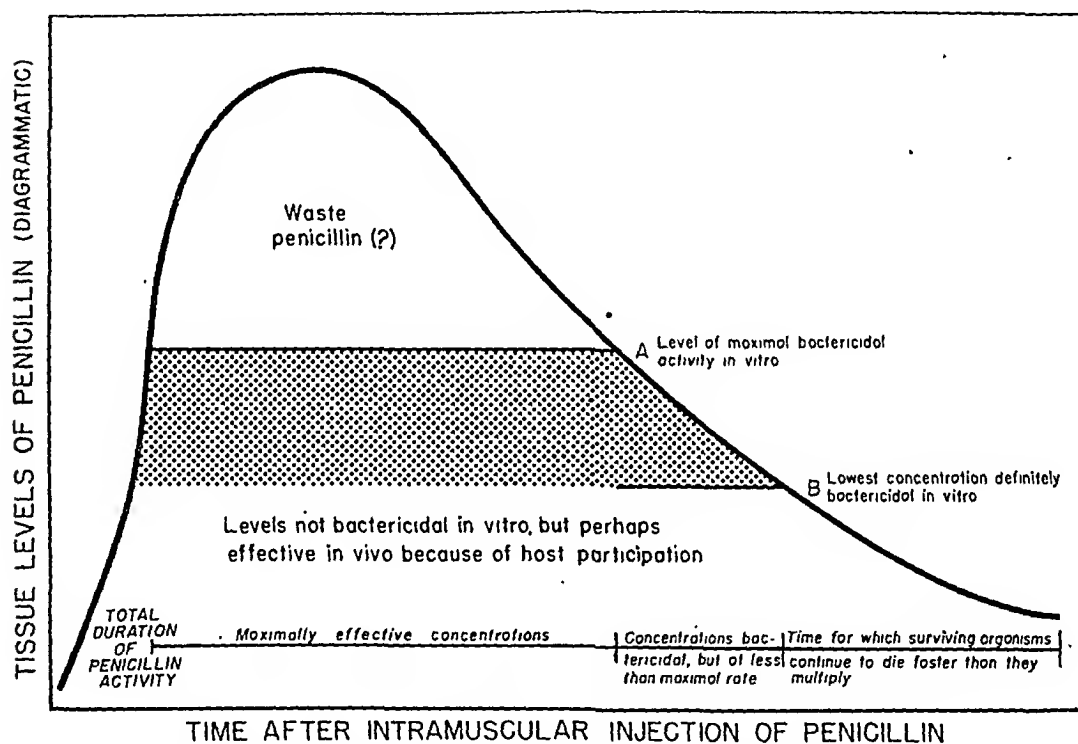


FIG. 6. A diagrammatic representation of the tissue concentrations of penicillin after its intramuscular injection in aqueous solution, considered in relation to the bactericidal activity of these concentrations.

Penicillin levels A and B correspond to those in figure 2: A is that which is maximally effective *in vitro*, and B is the smallest concentration which effects a net reduction *in vitro* in the number of viable organisms.

it has disappeared from the serum (cf. page 263); whether organisms exposed to penicillin may die as the result of that exposure long after the penicillin has disappeared from the surrounding fluid; or whether bacteria exposed to minimal concentrations of penicillin are thereby rendered more vulnerable to the body's normal defense mechanisms, so that concentrations ineffective *in vitro* may nevertheless be effective *in vivo*, are points for further study.²⁶

In summary, the activity of penicillin is probably determined by a composite of three time periods: the time for which it is at maximally effective concentrations; the time for which it is at concentrations which have a defi-

nite if slower bactericidal action; and the as yet indeterminate but quantitatively significant period, after penicillin has fallen to levels not bactericidal in vitro, during which some of the bacteria continue to die at a faster rate than the other reviving survivors can multiply.

One final point cannot here be considered in detail, but is relevant to this present discussion. With organisms which are killed most rapidly at a narrow optimum zone of penicillin concentration,⁸ and which die only slowly at concentrations in excess of this optimum level, aqueous injections of penicillin may be an inefficient method of treatment, since the optimally effective level is then provided for a relatively short time. Such organisms are killed only slowly while the penicillin is present in large excess; the rate of killing increases rapidly as the tissue concentrations approach the range of optimal concentration; and the rate falls off again as the concentration falls below the effective level. With such organisms, the most effective method of treatment may well be either (a) the administration of penicillin in oil and beeswax, or (b) a continuous intramuscular or intravenous infusion at a rate calculated to maintain the tissue concentrations at approximately that optimal level. The latter is technically more difficult, but susceptible of more precise control.

IV. IS IT NECESSARY TO MAINTAIN THE BLOOD AND TISSUE CONCENTRATION OF PENICILLIN AT BACTERICIDAL LEVELS?

It is clear from the preceding paragraphs that the penicillin levels in the blood may temporarily fall below those which are bactericidal in vitro without prejudicing the outcome of treatment. It is, however, equally clear that this "penicillin-free" interval between injections cannot be unduly prolonged without permitting the regrowth of the surviving organisms to such a degree as to counteract the therapeutic effect of the preceding injection of penicillin. The maximum time for which penicillin may be permitted to fall below effective levels without affecting the outcome of treatment will vary with the recuperative power of the particular organism and its normal rate of multiplication. An instructive contrast in this respect is afforded by experimental infections with *T. pallidum* and *Diplococcus pneumoniae* type I (figures 7 and 8).

The division time of *T. pallidum* in rabbits has been estimated, on the basis of the varying incubation periods after inocula of varying size, to be on the order of 30 hours.²⁷ This is to be compared with an observed division time in vitro of 10 hours for the cultured Reiter strain of *T. pallidum*.²⁸ Corresponding to this slow rate of multiplication, when syphilitic rabbits were treated intramuscularly with 16 doses of penicillin in aqueous solution, it was found that it made only a slight difference in its therapeutic activity whether the material was administered every four hours, twice daily, or even daily.²⁹ The total curative doses on these three schedules were 4000 (approximately), 1770 and 4000 units/kg.; and a dose of 250 units/kg. per

injection cured 50, 100 and 57 per cent of the animals, respectively. Since the latter dosage of 250 units/kg. provided a measurable level (0.03 unit) in rabbits for significantly less than two hours, it follows that when it was given only once daily, for at least 20 hours out of the 24* the blood and tissues

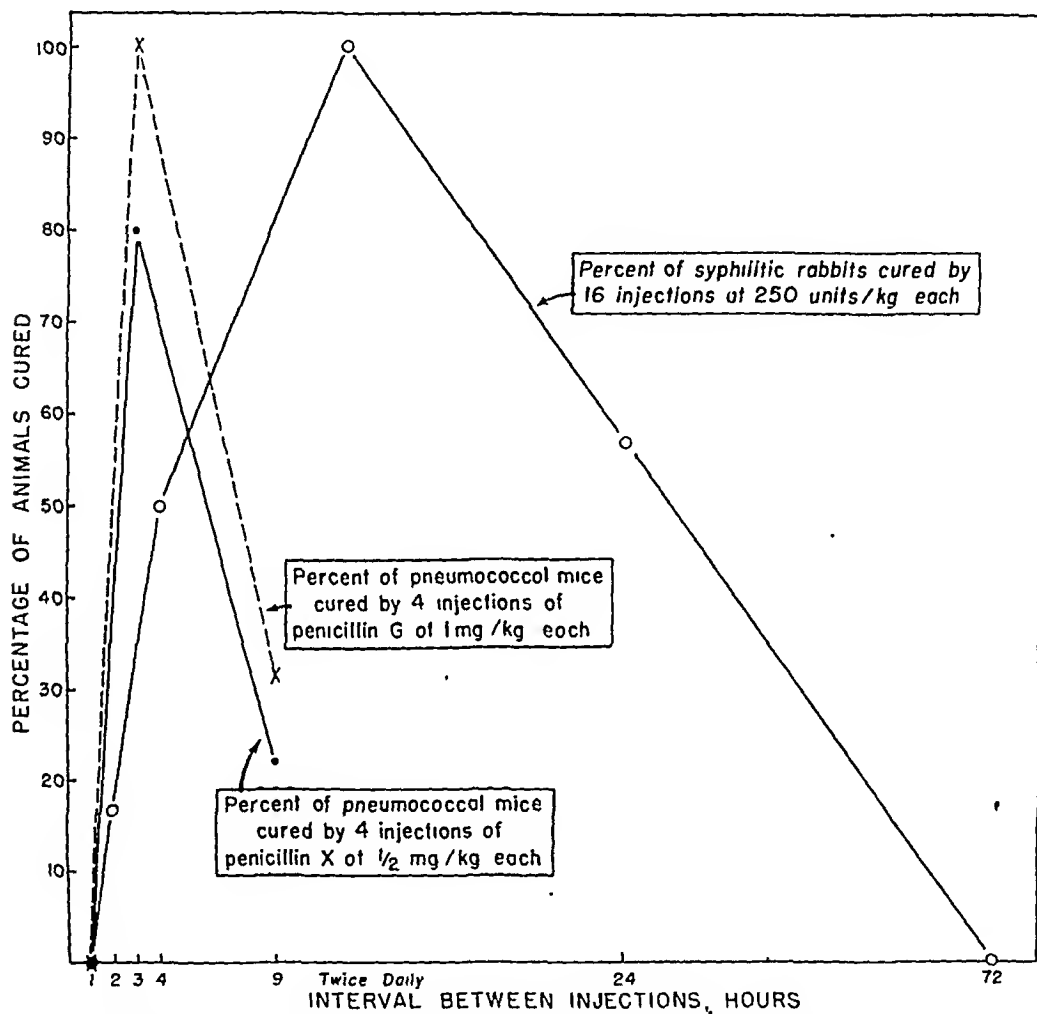


FIG. 7. The effect of the interval between injections on the therapeutic efficacy of a given dose of penicillin.

In pneumococcal infections of white mice, penicillins G or X administered at 9-hour intervals were far less effective than the same dosages administered at 3-hour intervals, due to the rapid re-multiplication of survivors in the penicillin-free interval. In the case of syphilitic infection, however, and reflecting the slow multiplication of the organisms, the interval between injections could be prolonged to 24 hours without abolishing the therapeutic efficacy of the drug. With even longer time intervals between injections, however, the organisms multiplied sufficiently in the penicillin-free interval to counteract the effect of the preceding injection.

contain insignificant and probably ineffective concentrations of penicillin. Nevertheless, the surviving organisms multiplied so slowly that even in this

* Allowing as much as two hours for the period during which surviving organisms might continue to die faster than they multiplied, after the serum level of penicillin had fallen to less than the concentrations which are effectively treponemicidal in vitro.

20-hour "penicillin-free" period there was insufficient growth to affect the therapeutic activity of the preceding injection of penicillin. If, however, the interval between injections was still further prolonged, to e.g. three days, there was then ample time for multiplication, and the previously effective dose of 250 units/mg. was now wholly ineffective.³⁶ Indeed, on this twice

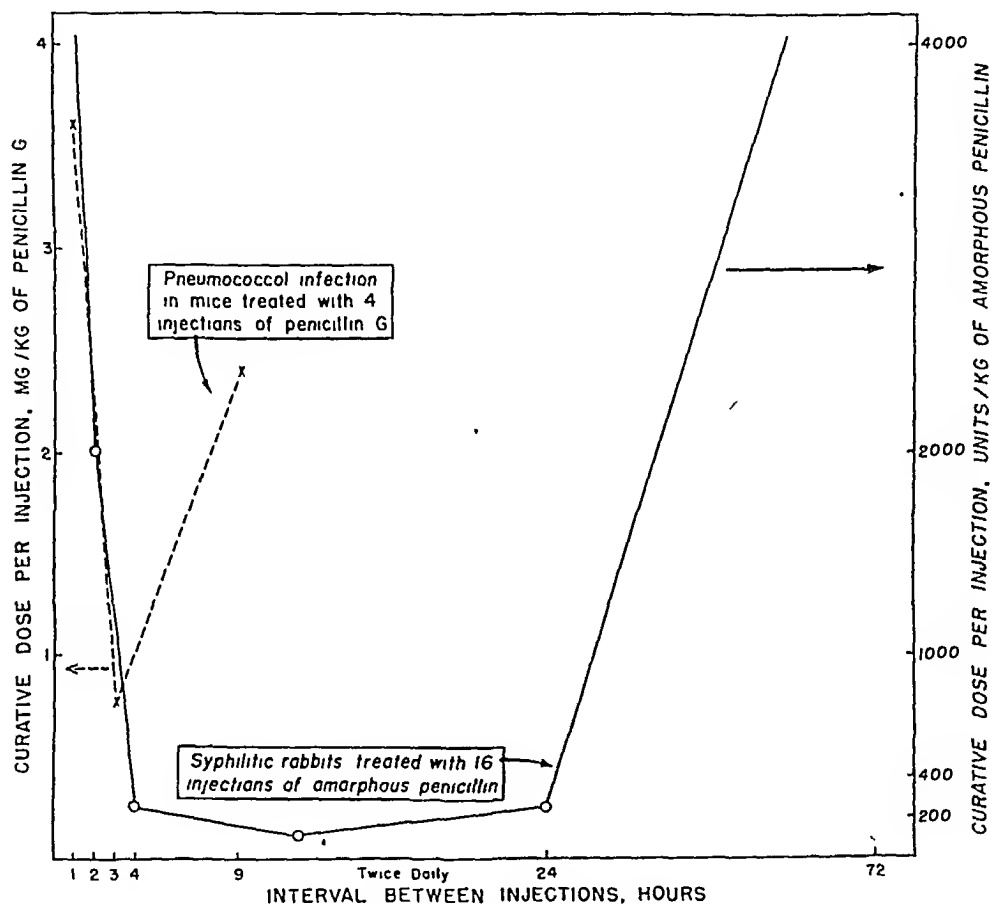


FIG. 8. The effect of the interval between injections on the curative dose of penicillin.

In pneumococcal infections of white mice, penicillins G or X administered at 9-hour intervals were far less effective than the same dosages administered at 3-hour intervals, due to the rapid re-multiplication of survivors in the penicillin-free interval. In the case of syphilitic infection, however, and reflecting the slow multiplication of the organisms, the interval between injections could be prolonged to 24 hours without abolishing the therapeutic efficacy of the drug. With even longer time intervals between injections, however, the organisms multiplied sufficiently in the penicillin-free interval to counteract the effect of the preceding injection.

weekly schedule even dosages of 2000 units/kg. per injection failed to cure any of the animals.

A precisely similar situation was observed in the treatment of type I pneumococcal infections in white mice; but with this organism, since the average division time of the organism during the phase of active growth was 30 to 40 minutes, instead of 10 to 30 hours,²⁸ the maximum time for which

the penicillin blood and tissue levels could be permitted to remain below effective levels without affecting the outcome of treatment was correspondingly short. As shown in table 3, and figures 7 and 8, much larger doses were

TABLE III

The Effect of the Interval between Injections on the Curative Dose of Penicillins G and X in Pneumococcal Infections of White Mice (after Eagle³⁵)

No. of injections	Interval between injections, hours	Penicillin G CD ₅₀ , mg./kg.*		Penicillin X CD ₅₀ , mg./kg.*	
		per injection	total	per injection	total
Four	1	3.1	12.3	1.3	5.2
	3	0.8	3.2	0.32	1.3
	6	2.6	10.4	—	—
	9	2.4	9.6	0.85	3.4
	24	14.2	56.8	—	—

* Calculated after Reed and Muench.

necessary to effect cure if the injections were given at nine-hour intervals than if they were repeated at three-hour intervals. Thus, when penicillin G was given every three hours for a total of four injections, a dose of 1 mg./kg. cured 80 per cent (12/15) of the animals; but that same dose given at nine-hour intervals cured only 30 per cent (2/9). With penicillin X injected at three-hour intervals a dose of 0.5 mg./kg. cured all the animals tested (15/15); but given at nine-hour intervals, that dose cured only 33 per cent (5/15). As shown in figure 9, with both penicillins G and X, the curative dose (CD₅₀) on the nine-hourly schedule was two and a half to three times greater than on the three-hourly schedule. (The low therapeutic activity of injections repeated at one-hour intervals will be discussed in a following paper.)

In mice, penicillin G injected at 1 mg./kg. remains in the plasma at levels effectively pneumococidal in vitro for approximately 1½ hours. When these doses were given at three-hour intervals, the "penicillin-free" interval was therefore on the order of 1½ hours; and in this period the organisms surviving the effects of the penicillin did not recover and multiply sufficiently to counteract the rapid bactericidal action of the drug (in vitro, 97 per cent killed in one and a half hours).²⁸ However, when the injections were given at nine hour intervals, the penicillin-free interval was then approximately 7½ hours. This permitted the surviving organisms to recover from the toxic effects of their brief exposure to penicillin, and to multiply sufficiently to counteract the bactericidal action of the drug. On this nine-hour schedule, one had to give three times as much penicillin to obtain the same results as on the three-hour schedule. It is a reasonable surmise that

the larger doses were effective, not by virtue of the higher blood levels they afforded, but because effective levels would then be provided for longer periods of time. More organisms would then be killed by each injection, fewer would be left to multiply during the penicillin-free interval, the duration of that interval would be reduced, and the balance would be restored in favor of the therapeutic agent.

In summary, although penicillin need not be maintained continuously at effective levels in order to effect cure, the maximum length of time for which those levels may be permitted to fall below concentrations which are bactericidal in vitro will vary from organism to organism. The "penicillin-free" interval between injections may contribute to therapy, but only so long as some of the surviving organisms continue to die, by whatever mechanism, at a rate exceeding that at which the others re-multiply. Once that therapeutically favorable balance is reversed, and once the rate of multiplication catches up with the rate at which the organisms can be destroyed, then the longer the time interval before the next injection of penicillin, the greater will be the degree to which the interim re-multiplication of organisms has counteracted the therapeutic effect of the preceding injection.

V. SCHEDULES OF TREATMENT WITH PENICILLIN WHICH WILL MAINTAIN THE SERUM CONCENTRATION IN EXCESS OF A GIVEN LEVEL^{9, 31, 34}

In the light of the foregoing discussion, in the treatment of bacterial infections with penicillin it may be desirable to know the average time period for which a given dose would provide serum concentrations in excess of a given value; or conversely, how often a given dose of penicillin must be repeated in order to maintain that serum level. Such data can be used only as a rough guide to treatment in view of the large and varying differential between the serum concentration of penicillin and that at the focus of infection (cf. page 265); but by and large, the provision of a 2- to 10-fold excess in the serum will assure the presence of the maximally effective level in most tissues.

Figure 3 (after⁹) shows the average blood levels after the intramuscular administration of aqueous penicillin G at dosages of 10, 3, 1.5, and 0.6 mg./kg., corresponding to total dosages of 1,200,000, 360,000, 180,000 and 72,000 units in the average adult. In table 4 (from⁹) these data have been used to calculate the dosage of penicillin necessary to sustain a serum concentration in excess of a given level for a period of one, two, or four hours. Finally, table 5, also after Tucker and Eagle,⁹ indicates the frequency with which a given injection should be repeated in order to maintain a given plasma level. Thus, as shown in vertical column 8 of that table, in order to assure the constant presence of at least 1 microgram (1.6 units) per c.c., one may inject 720 mg. (1,200,000 units) every three to four hours, 360,000 units every 2 hours, or 180,000 units every hour.

At the present writing, similar tables and figures cannot be constructed for penicillin in oil and beeswax, and for two distinct reasons. The first is

the fact that with this preparation, there is greater variation among individual patients in the rate of absorption than is the case with the aqueous solutions. The second and more disturbing fact is that different commercial preparations of penicillin in oil and beeswax vary markedly in the length of time for which they provide a given serum level of penicillin.⁹

VI. RECAPITULATION AND DISCUSSION

The blood penicillin level is of significance insofar as it provides a rough measure of the concentration at the foci of infection in the tissues. The curve

TABLE IV

Amount of Penicillin G in Aqueous Solution Which Must Be Injected at Given Intervals in Order to Maintain a Desired Plasma Level (Tucker and Eagle⁹)

Interval between injections (hours)	To maintain a plasma concentration of penicillin G in excess of							Micrograms per c.c. Units per c.c.
	0.1 0.16	0.2 0.32	0.5 0.8	1.0 1.6	2.0 3.2	5.0 8.0	10.0 16.0	
	the following dosages must be given at the intervals indicated in the left hand column (upper left hand figure in each block is dosage in mg./kg.; lower right hand figure is the total dose in units in average adult)							
1	0.16 20,000	0.35 40,000	0.74 85,000	1.3 150,000	2.1 250,000	4.2 500,000	9.1 1,000,000	
2	0.45 50,000	0.95 100,000	1.9 220,000	2.7 330,000	4.7 550,000	11.5 1,300,000	— —	
3	1.2 140,000	1.9 220,000	2.9 340,000	5.7 675,000	11.5 1,300,000	— —	— —	
4	2.0 235,000	2.8 330,000	7.4 855,000	11.4 1,300,000	— —	— —	— —	
6	5.2 600,000	8.8 1,000,000	— —	— —	— —	— —	— —	
8	12.0 1,400,000	— —	— —	— —	— —	— —	— —	

of those tissue levels after an injection of penicillin is probably of major importance in relation to its therapeutic efficacy, and may be expressed in terms of three time periods: the length of time for which penicillin is present at maximally effective concentrations which kill the organisms at the fastest possible rate; the time for which penicillin is present at somewhat lower concentrations, which are more slowly bactericidal; and finally, the time period, after the penicillin has fallen to concentrations lower than those which kill the bacteria in vitro, but during which the organisms continue to die in vivo at a rate faster than they multiply. Whether this continuing death in the apparently penicillin-free interval is due to the fact that penicillin persists in the tissues longer than it does in the blood; whether organisms are killed by lower concentrations of penicillin in vivo than they are in vitro, due to the participation of the body's defense mechanisms; or whether organisms exposed to penicillin recover from its toxic effects only slowly, and during that

temporary period of retarded multiplication are disposed of by the cellular and humoral defense mechanisms of the host, are as yet open questions.^{20, 32} In any event, this third period of gradually disappearing penicillin activity provides a margin of safety, in that the blood and tissue penicillin levels may be permitted to fall below those which are significantly bactericidal in vitro without affecting the outcome of treatment.

TABLE V

Frequency at Which a Given Dose of Penicillin G in Aqueous Solution Must Be Injected in Order to Maintain a Desired Plasma Level (Tucker and Eagle⁹)

Micrograms per c.c. Oxford Units per c.c.				To maintain a plasma concentration of penicillin G in excess of						
				0.1 0.16	0.2 0.32	0.5 0.8	1.0 1.6	2.0 3.2	5.0 8.0	10.0 16.0
Dosage per kg.		Total dose in average adult		the injections indicated in the left hand column should be repeated at the intervals (hours) indicated in the body of the table						
mg.	units	mg.	units							
10	16,700	720	1,200,000	8.0	6.0	4.5	3.5	3.0	2.0	1.2
3	5,000	216	360,000	5.0	4.0	3.0	2.0	1.6	0.6	—
1.5	2,500	108	180,000	3.0	2.5	1.7	1.2	0.8	—	—
0.6	1,000	43	72,000	2.0	1.5	0.8	—	—	—	—
0.3	500	22	36,000	1.6	0.9	—	—	—	—	—
0.15	250	11	18,000	0.9	—	—	—	—	—	—

Eventually, however, the surviving organisms do recover from the toxic effects of penicillin to the degree that they multiply faster than they can be killed, and thus counteract the effect of the preceding treatment. If this is permitted to continue for only a brief period before the injection is repeated, the effect of treatment is counteracted only in part. More organisms are killed by each injection than reappear between injections; and provided that treatment is continued for a sufficiently long period of time, the patient may ultimately recover. If, however, too long an interval is permitted between injections, the effect of treatment may be wholly counteracted by the intervening re-multiplication of the surviving organisms. As has been indicated in the present paper, the danger is greater with organisms which recover rapidly from the toxic effects of penicillin, or which multiply at a fast rate, than it is in the case of organisms which multiply only slowly (*T. pallidum*).

Large injections of penicillin are more effective than small injections, not because they provide higher absolute levels of penicillin, but because they provide the effective concentrations for longer periods of time. More organisms are then killed by each injection, and fewer survive to re-multiply in the interval between injections. Further, that interval may then be prolonged, because with fewer surviving organisms, less harm is done by a penicillin-free interval of multiplication.

It is obviously not necessary to maintain the blood and tissue concentrations of penicillin continuously at effective levels in order to attain cure. The most rapidly effective method of treatment would nevertheless be to repeat injections at such frequency as to maintain the tissue levels continuously in excess of that concentration which kills organisms at the maximum possible rate. (This could be achieved also by continuous intravenous, intramuscular or subcutaneous infusion at a rate designed to maintain at the focus of infection that level maximally effective for the specific organism.) However, this generalization requires qualification in at least two respects.

The first is the possibility suggested by Bigger³³ that, since bacteria are killed by penicillin only while they are multiplying, a continuously maintained level of penicillin may fail to kill those organisms which happen to be present in a physiologically inactive resting phase. Those hypothetical resting organisms ("persisters") would become vulnerable to the action of penicillin only if they were permitted to resume multiplication. Bigger suggests that intermittent treatment might therefore be more effective than continuous treatment, since the persisters would resume multiplication in the penicillin-free interval and thereby become vulnerable to the succeeding injection of the drug. There has as yet, however, been no convincing demonstration in either animals or men that intermittent treatment, i.e., periods of effective concentrations separated by penicillin-free intervals, are in fact more effective than continuously maintained levels.

The second qualification is due to the fact that certain organisms are killed more rapidly at low concentrations of penicillin than they are at high concentrations.⁸ All of four strains of group B β -hemolytic streptococci, two of four strains of group C organisms, five of seven strains of *Streptococcus fecalis*, three of four strains of other α -hemolytic streptococci, and four of nine strains of staphylococci were found to give this paradoxical zone reaction. With such organisms, a continuously sustained level provided by a continuous intravenous or subcutaneous infusion might therefore be more effective therapeutically than the rapidly changing blood levels afforded by intramuscular injections of penicillin in large dosage, since with the latter method the optimally effective concentration would be present for only a short period of time.

If the thesis elaborated in the present paper is correct, then the therapeutic activity of a given dosage of penicillin rests in large part, if not primarily, on the total length of time for which it remains at bactericidal levels, with particular emphasis on the time for which it is present at the maximally effective concentration, plus the time required for the organisms to recover from the drug and effectively resume multiplication. The enormous differences observed in the curative dose of penicillin when either the number of injections or the interval between them is varied,²⁹ should rest primarily on the total time period of effective penicillin action.⁵ Conversely, different schedules of treatment which have the same biological effects (e.g. 50 per cent cure in a

given infection) should provide effective levels for the same total period of time,* whether the curative dose on those equi-effective schedules is 200,000 or 200 units/kg. An experimental demonstration of this relationship will be discussed in a following paper.³⁵

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PSYCHIATRIC ASPECTS OF VAGOTOMY: A PRELIMINARY REPORT *

By THOMAS S. SZASZ, M.D., *Chicago, Illinois*

INTRODUCTION

THERE has been a great deal of interest in vagotomy, as a therapeutic technic for peptic ulcer, ever since its introduction by Dragstedt ¹ four years ago. Several excellent papers have appeared subsequently on the indications, physiologic effects, and clinical results of this treatment.^{2, 3, 4, 5, 6, 7} However, no report has appeared in the literature, to date, on any systematic psychiatric studies of patients subjected to vagotomy. Due to the interest and helpful coöperation of Dr. Lester R. Dragstedt and Dr. Walter L. Palmer a study of a number of such patients was made possible. This study has now been in progress for approximately eight months, a rather brief period for a project of this type. However, certain preliminary conclusions can be formulated which are considered of sufficient interest to warrant presentation at this time.

CLASSIFICATION OF CASES

This preliminary report is based on a study of 16 patients. All patients but one were referred routinely; one individual was referred because of symptomatic psychiatric difficulties. Detailed anamneses were obtained from all patients and most were seen in more than a single interview; five of the patients were studied in great detail, each having been seen in 10 or more interviews. All but one of the patients were men. In age, they ranged from 23 to 65 years. The duration of the ulcer symptoms ranged between three and 45 years. There was roentgen evidence of ulcer, before vagotomy, in all of the patients. Only one had a gastric ulcer; in the remaining 15 the ulcer was in the duodenum. Eleven patients were seen only after vagotomy, and five both before and after. The operation performed in each case was a subdiaphragmatic vagotomy; a gastroenterostomy was also done in all but one of the patients. Except for one patient who was operated upon in June 1945 and who was subsequently referred because of psychiatric illness, all the others were operated upon between June 1946 and February 1947; the period of follow-up on these patients thus ranges from two to 10 months.

RESULTS

It seemed best to consider the results following vagotomy from two different points of view; the data were therefore analyzed in an attempt to answer the following two questions:

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From the Division of Psychiatry, Department of Medicine, University of Chicago.

1. What happens to the ulcer?
2. What happens to the patient?

At present it is possible to answer the first question with some degree of definiteness. If the section of the vagi is complete, the ulcer heals and apparently does not recur.^{3, 4} This has been true for approximately 200 patients operated upon by Dragstedt⁵ during the past four years.* In the present series, the ulcer has healed and has not recurred, up to the present time, in 15 out of the 16 cases. The patient whose ulcer has not healed yet was operated upon in January 1947; two months later, the ulcer crater, though of decreased size, was still demonstrable roentgenologically in the pylorus. The possibility of malignancy could not be ruled out, and this patient is under close observation at the present time.

The answer to the second question, namely, "What happens to the patient?" is a tentative one and is based largely on observations in this series of cases. The results have been classified under three clinical headings; this was based essentially on (a) whether or not the patient developed other symptoms following vagotomy, and if so, the nature, severity, and incapacitation suffered therefrom, and (b) the nature of the patient's social adjustment following vagotomy.

TABLE I
Results

	Number of Patients	Per Cent
1. Improved	9	57
A. Good results	6	38
B. Fair results	3	19
2. "Status quo ante"	6	37
3. Poor results	1	6
Total	16	100

For criteria employed in evaluating results see text and footnote, page 281.

1. *Improved.* Nine of the 16 patients fall into this group, which has been further subdivided as follows:

A. *Good results.* Six patients have resumed their former occupations and are free from gastrointestinal as well as other symptoms.

* The first and only patient with what was thought to be a complete vagotomy who developed a recurrence—or more precisely a new ulcer—came to our attention very recently. This man (W. C. B.), age 63, was the first patient to undergo supradiaphragmatic vagotomy in this hospital (January 1943). He was without gastrointestinal symptoms until about six months ago; he then noted recurrence of ulcer pain relieved by milk and antacids. Roentgen examination revealed a huge ulcer crater on the lesser curvature of the stomach. The results of the tests used to determine the completeness of the vagus section (insulin test and night secretion studies) indicated that the vagotomy was a complete one. On operation (April 11, 1947) a huge ulcer was found on the lesser curvature of the stomach and subtotal gastric resection was performed. At this operation, a nerve fiber to the stomach, thought to be part of the vagus, was found and excised; histological study of this specimen showed intact nerve fibers; it is thus questionable whether or not this patient has had a complete vagotomy. Histological examination of the ulcer showed no evidence of malignancy. It is of interest to note that prior to vagotomy the patient's ulcer was in the duodenum.

B. *Fair results.* Three of the 16 patients fall into this group in which were included patients who are not entirely free of symptoms but in whom vagotomy was, on the whole, of benefit. (For the purposes of this classification the common, early post-operative symptoms of fullness after eating, "bloating", and slight diarrhea have been disregarded; these are, apparently, primarily physiologically determined and usually disappear in a few months.) Two patients in this group were annoyed by an increased frequency and intensity of feelings of hunger; one of them found it necessary to drink warm milk, every night, before he could fall asleep; and occasionally he drank some milk between meals. He had no ulcer symptoms.

2. "*Status quo ante.*" Patients in this group, though completely healed of their ulcer (except for one, referred to earlier, whose ulcer has not yet disappeared completely) continued to have some type of difficulty; some complained of symptoms closely resembling those which they experienced prior to vagotomy; others developed new symptoms of approximately equal severity. From the point of view of the patient as a whole, except for the healing of the ulcer, the status of these individuals was essentially unchanged by vagotomy.* Six patients fall into this group. Five individuals continued to complain of various abdominal symptoms; and three of these were relieved by milk and/or dietary restrictions (sometimes self-imposed). One patient became a heavy drinker.

3. *Poor results.* Only one patient in this series falls into this group; he is the one who was referred because of psychiatric illness. This man, though his ulcer is healed, is completely incapacitated socially. He is a 49 year old engineer who had had a duodenal ulcer for 17 years before he was operated upon. There was a history of a period of addiction to opiates, four years prior to vagotomy. This patient developed hysterical conversion symptoms four months after operation; he also resumed taking opiates whenever he could obtain any; and his total behavior was one of intense infantile dependence; he was a psychological invalid. Seventeen months following vagotomy he still felt unable to work, and when last heard of he was getting "treatments" from a chiropractor.

In evaluating the results it must be borne in mind that the period of follow-up has been rather short; the error, therefore, is likely to be in favor of the first group.

PSYCHOLOGIC FACTORS IN PEPTIC ULCER

In order to make this analysis more meaningful as well as to more clearly evaluate vagotomy from a psychiatric point of view, we must consider briefly our concepts concerning the rôle of psychologic factors in the pathogenesis of peptic ulcer. Unfortunately space does not permit a detailed con-

* This statement does not give sufficient consideration to the healing of the ulcer per se, and thus the prevention of potential complications (e.g., hemorrhage, perforation) from this source alone. This prophylactic value of vagotomy does not find expression in the above classification of results.

sideration of this subject.^{9, 10, 11, 12, 13, 14, 15} The psycho-physiologic chain of events which may lead to the formation of a peptic ulcer is shown in a simplified and schematic form in table 2. This is based largely on Alexander's work.^{9, 10} As shown in this table, it is the conflict between powerful dependent needs and strivings for independence, and the regressive solution of this conflict in the face of frustration of the "receiving" tendencies, which is of crucial importance for the development of an ulcer.

TABLE II

Probable Chain of Events in the Pathogenesis of Peptic Ulcer

- I. Conflict (Unconscious)
- | | | |
|------------------------------------------------------------------------|-----------------------|------------------------------------------------------------------------|
| Dependence
("Being taken care
of like an infant")
"Receiving" | \longleftrightarrow | Independence
("Taking care of others
like an adult")
"Giving" |
|------------------------------------------------------------------------|-----------------------|------------------------------------------------------------------------|
- II. Frustration of dependent needs
1. Internal (superego)
Dependent tendencies are ego-alien (unacceptable)
 2. External (reality)
Patient would accept dependent rôle but he is, in reality, not a child any more; society demands adult rôle.
- III. Regression
1. Psychologically: return to the level of the suckling infant; love and security are equated specifically with feeding, and more generally with "receiving."
 2. Physiologically: stomach is in an almost continuous state of preparation for receiving food; it "behaves" like the stomach of the suckling infant. This state of affairs is brought about (mediated) by a hypertonus of the secretory and motor fibers of the vagi.
- IV. End Result
- Morphological change in the upper gastrointestinal tract: peptic ulcer.

Let us now compare the time-tested medical therapies for peptic ulcer¹⁶ with vagotomy, in the light of what is known about the rôle and significance of psychologic factors in this disease. From the physiologic point of view, there are certain basic similarities between these two anti-ulcer therapies. Both attempt to influence the increased and continuous secretion of acid gastric juice. Frequent feedings, milk, cream, and antacids accomplish this by buffering (neutralization) of the acid. Vagotomy achieves a similar end result by a fundamentally different method: the neural pathway which mediates the increased gastric secretion is sectioned. Gastric acidity—and particularly the night secretion—is thus reduced; the altered gastric motility also may be of some significance in the healing of the ulcers.

Consideration of the physiologic effects of these two fundamental approaches to the treatment of peptic ulcer, however, gives no inkling about the psychologic aspects of the problem. It must always be borne in mind that whatever therapeutic technic may be used—be it bed rest, diet, chemotherapy, or surgery—it has certain psychological *meaning* to the patient.¹⁷ This aspect of the treatment is of particular importance in peptic ulcer. As indicated earlier, these patients have a great need to "receive"; and incorporation via the gastrointestinal tract is particularly meaningful to them. As a

matter of fact, experienced physicians frequently understand this intuitively. For example, it is well known that many ulcer patients experience striking relief of their symptoms as soon as they are hospitalized, even though essentially the same medical regime is continued as was used at home. A recent article in *Lancet* by A. M. Gill¹⁸ will further amplify this point about the *meaning* of therapy. He writes: "A consecutive series of 20 patients, each with a chronic gastric ulcer, were given a daily hypodermic injection of 1 c.c. of distilled water. They were ambulant, their diet was unrestricted and even disregarded, they were given no medicines, and those who enjoyed smoking were encouraged to continue. With one exception all lost their pains as quickly—i.e., within a few days—as a control series treated along orthodox lines. Healing of the ulcers was observed gastroscopically and took place in the usual time—i.e., in four to eight weeks from the start of treatment." What does all this mean? It means simply that being in a hospital or getting "shots" *means* something to the patient, something which is very important. Just as in everyday language we can differentiate between the denotation and the connotation of a word—so in therapy, medical or surgical, we should think of the "connotation" of our specific therapeutic technic. In other words, we should consider the *unconscious meaning of the procedure to the patient*.

This brings us to the important difference between the medical management of ulcer and vagotomy. The frequent ingestion of milk and cream does more than just buffer (neutralize) free acid; it has the meaning of actually receiving food, and unconsciously this stands for affection and security. The close resemblance of the Sippy regime to the feeding schedule of the young infant has been pointed out many times before, but its significance cannot be overemphasized. This, however, should not be confused with what is called the "secondary gain" in neurosis; we are referring to the symbolic and unconscious meaning of the therapy—the satisfaction of an emotional (instinctual) need.

In contrast to the above, vagotomy brings about the physiological changes necessary for the healing of the ulcer without providing any gratification for the patient's needs to "receive." It therefore seems especially significant that the ulcers heal, and do not recur, in spite of the fact that these important emotional needs remain ungratified and the basic conflict remains unchanged. From the purely physiologic point of view, this is only further evidence for the fundamental soundness of vagotomy in abolishing the ulcer. From the psychiatric as well as from the general clinical point of view, however, an important disadvantage of vagotomy may lie in this very absence of providing gratification for the patient's dependent (oral) needs. This is illustrated by several patients: three in the present series, and one reported by Moore and his associates in a recent paper. The three patients in this series obtained relief from abdominal pain and discomfort by drinking milk, even though their ulcers were healed. And Moore⁶ writes: "The fifth (patient), while

clear of disease roentgenologically, is now two years postoperatively, again taking antacids and milk for 'ulcer pain.'” The meaning of this self-treatment should be clear in the light of the foregoing discussion. Freud has admonished us always to pay attention to what the patient tells us; and if these patients tell us that they need milk—we should listen, even if they do not have an ulcer any longer! Their continued need for, and insistence on, milk and antacids is an important clue to our understanding of the problem of peptic ulcer.

Our understanding of the pathogenesis of peptic ulcer has been helped considerably by the study of vagotomized patients. The evidence very strongly suggests that man does not develop peptic ulcer * if the vagi are completely sectioned. Among all of the patients operated upon by Dragstedt there has not been a single instance of recurrence, if the vagus section was complete; † a truly amazing record.

That emotional stimuli are mediated from the central nervous system to the stomach via the vagi is not a new concept. In 1936, Alexander¹⁰ stated: “Obviously the psychic stimulus is led to the stomach through parasympathetic pathways.” The evidence for this is now conclusive:

1. The ulcers heal and do not recur following vagotomy. This occurs in spite of the persistence of the emotional conflicts etiologically related to the production of ulcer in the intact human being.

2. There is a reduction in the volume and acidity of the continuous night secretion to normal, following vagotomy; the response to sham feeding is abolished.

3. In one of our cases we demonstrated a marked increase in the acid gastric secretion when the patient experienced anger; this effect was abolished by vagotomy.¹³

COMMENT

In conclusion, let us consider the therapy of peptic ulcer from the psychiatric point of view—or to put it differently—from the point of view of the patient as a whole. In considering this problem, Alexander, in “The Medical Value of Psychoanalysis,”¹⁰ stated: “Undoubtedly in all psychogenic cases only psychoanalysis can be considered as an etiological therapy, because in the long chain of events that finally lead to ulcer formation, the chronic psychic stimulus (the repressed wish to be loved, to be fed) is the first link.” And Dragstedt,³ in a recent paper, wrote as follows: “The central nervous

* The term “peptic ulcer” is used to denote the “usual clinical case” of peptic ulcer; cases of either Cushing’s ulcer^{19, 20} or Curling’s ulcer²¹ are not to be included under this heading. Vagotomized patients, of course, could not be expected to develop a Cushing’s ulcer. The development of Curling’s ulcers on the other hand cannot be expected to be preventable by vagotomy; however, we know of no report in the literature, to date, of such a case, in a vagotomized person. Ulcers have been produced in vagotomized animals (dogs, cats, and rabbits) with histamine.²²

† This statement may have to be modified somewhat in the light of recent experience; see footnote, page 280.

system disturbance causes ulcers by producing a hypertonus in the secretory and motor fibers in the vagus nerves. While the severing of these nerves prevents nervous tensions of various kinds from affecting the stomach, it cannot be considered the final answer to the ulcer problem. Perhaps this may lie in adjusting the individual to his work and environment so that these tensions do not arise."

Most psychiatrists now believe that emotional factors are of paramount etiological importance in a very large percentage of cases of peptic ulcer. That not all patients can be, or even need be, subjected to psychoanalysis is obvious²³; perhaps the briefer methods of psychoanalytic therapy will prove to be of practical help to an ever increasing number of patients.^{24, 25} Still, it must be remembered that most patients with peptic ulcer are now and, probably for a long time to come, will be treated by the general practitioner, the internist, the gastroenterologist, and the surgeon. What recommendations can the psychiatrist offer regarding the treatment of these patients in general, and vagotomy in particular? We want to preface our suggestions by restating the belief that the optimum treatment for patients with peptic ulcer is psychoanalytic therapy. This conclusion follows inevitably from our concept of the disease; in most cases the lesion in the upper gastrointestinal tract is but one manifestation of an emotional illness involving the total personality. The question, however, which must be answered at this time is, "How to manage patients who, for whatever reason, will not be treated psychotherapeutically?" Further comments will apply to this group of cases only.

Since many patients with uncomplicated peptic ulcer respond so readily to even simple medical regimens, it would seem best to treat such patients conservatively. Vagotomy, however, has, and will continue to have, an important place in the treatment of peptic ulcer. It is certainly the most physiological of all the surgical procedures used in the treatment of this disease. Section of the vagi interrupts the "final common pathway" in the chain of events leading to the formation of ulcer. There seems to be no more direct, nor more effective technic, at the present time, for bringing about the healing and the prevention of peptic ulcer. Almost any patient, therefore, in whom the ulcer cannot be made to heal, or cannot be prevented from recurring, with the usual medical measures of diet, milk and cream, and antacids, may benefit from vagotomy (except when the procedure is contraindicated for specific medical or surgical reasons).^{6, 26} Even symptomatic (i.e., other than ulcer) psychiatric illness is, per se, not a contraindication to vagotomy. It should be emphasized, however, that the abrupt discontinuation of medical measures may be psychologically harmful to these as well as to many of the other patients. The value of vagotomy is now well established and it is therefore no longer necessary to instruct patients to discontinue all pre-operative medical measures—which, true enough, physiologically they no longer need, but which may continue to help them greatly psycho-

logically. This is particularly true of the taking of milk which becomes a habit with many ulcer patients. We would advocate that patients be permitted to continue with such "medical" measures for some time following vagotomy, and if need be indefinitely. ("Weaning" should not be abrupt!) A combination of the unmatched physiologic advantages of vagotomy with the psychologically meaningful aspects of the usual medical anti-ulcer measures may yet prove to be the best (non-psychoanalytic) method of therapy for these patients.

SUMMARY

The clinical results in a group of patients studied carefully from the psychiatric point of view and operated upon for peptic ulcer by resection of the vagi are presented.

In all cases but one the ulcers have healed and there have been no recurrences, to date, in the present series. Clinical results, however, cannot be based on the fate of the lesion in the gastrointestinal tract alone. In answer to the question, "What happens to the patient, as a whole, following vagotomy?", the following answer was found. A little over half (57 per cent) of the patients in this series have been definitely helped by vagotomy. Six patients (37 per cent) were found to be "status quo ante," from the psychiatric and clinical points of view; the healing of the ulcer, however, confers protection on these patients against future complications from this source (e.g., hemorrhage, perforation). This prophylactic value of vagotomy does not find expression in our present classification of results. One patient became definitely worse following vagotomy and remained incapacitated (psychologically) during the period of observation.

The rôle of psychologic factors in the pathogenesis of peptic ulcer is discussed. Patients suffering from this illness have a strong need to "receive." These receptive-acquisitive tendencies obtain some (partial) gratification from the usual medical measures used in the treatment of peptic ulcer; vagotomy brings about healing of the ulcer without providing for these important emotional needs. This explains why some patients insist on continuing with some part of their medical regimen (e.g., taking milk) after vagotomy, when the physiologic needs for such treatment are no longer present.

Psychoanalysis is, in our opinion, the only etiologic treatment in most cases of peptic ulcer. This type of treatment, however, is of limited applicability and is not available for the large majority of patients at the present time.

For those patients who do not respond adequately to the usual medical ulcer regimens and who, for whatever reason, will not be treated psychoanalytically, vagotomy is probably the treatment of choice. The absence of symbolic oral gratification due to cessation of dietary and other medical measures following vagotomy is thought to be potentially harmful. It is

suggested that the clinical results may be improved somewhat if the patients are permitted (possibly even encouraged) to continue with certain psychologically meaningful aspects of their preoperative medical regimens after vagotomy.

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THE RÔLE OF ANXIETY IN SOMATIC DISEASE*

By MAXWELL GITELSON, M.D., *Chicago, Illinois*

I. STRUCTURE AND FUNCTION OF THE ANXIETY MECHANISM

ANXIETY reactions to organic disease follow the same principles as those which govern the generation of anxiety in general. In a given situation which constitutes a threat to the interests of an organism there occurs a somatic mobilization which is reactive to the danger and preparatory for coping with it. The most easily perceived effects of this are referable to the heart and the respiratory organs. Motor innervations also take part in this reaction. In the human being awareness of these events constitutes the actual unpleasant sensation of anxiety.

The mobilization of anxiety may be vestigial or quite complete. Thus there may be a transient epigastric sensation, a few extrasystoles, a sharp inspiration, and a slight tensing of the skeletal musculature. Or, the heart may assume a steadily increased force and rate, accompanied by increased ventilation, and vigilant exploratory activity. If the danger then materializes the organism is aware of and ready for the alternative—fight or flight. We see thus that anxiety is not merely a symptom. It has a very definite function in the interest of survival. It is, so to speak, a readying mechanism which clears the deck for action.

Beginning very early, human beings internalize the objects of the environment and the relationships which exist among them. Language function and the capacity for imagery make this possible. In consequence the anxiety mechanism operates in response to various types of psychic representations of danger.

II. DEVELOPMENTAL HISTORY OF THE ANXIETY REACTION

The dangers to which the human being responds with anxiety are derivatives of those which appear and have paramount importance at successive stages in the development of the personality.

At the very earliest stage, survival is the outstanding problem. The inability of the infant to do anything about this without assistance is obvious. The first anxiety situation is the powerlessness of the infant to cope with internal tensions produced by the needs arising from hunger, cold, pain, and postural insecurity. The first consequence of the mobilization of the anxiety mechanism is the helpless cry which, together with the unorganized movements of the infant, serves only to discharge tension.

At the next stage the child has made a more or less clear identification of

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the mother as the agent of the relief of tension. The leading danger situation then becomes the absence of the mother. The tensions belonging to hunger, or discomfort, need no longer be immediately present to produce the anxiety signal and the infant's cry. Separation from the mother is now enough. The infant's cry is no longer helpless but help-bringing. For the first time anxiety is seen to be functional rather than simply reactive to tension. Now the infant is able to govern its environment.

In consequence of the further maturation of the nervous system, the powers of perception improve and become integrated with the powers of manipulation and locomotion. More or less active mastery of the environment now becomes possible. The organism becomes more dependent on its own sensory-motor capacities to govern the environment in its interest. The complete elaboration of these capacities goes on until adulthood. With their first appearance, however, comes the anxiety which is connected with any threat to physical integrity. Any threat to the powers of overt activity now is tantamount to a threat of return to the helplessness and dependence which had previously characterized the state of the infant. The adaptive response to anxiety is now characterized by an attempt at physical mastery.

The maturation of the physical powers of mastery brings the individual to the final stage of integration, that which finds him in a social relationship to other people. The social structure, rather than the physical environment now establishes the criteria of survival. By means of the technics of the particular culture, the person now aims at success, security, status, and power. The anxiety stimulus now resides primarily in negative factors that militate against such attainments.

To these are added the burden of social disapproval of certain strivings. Such sanctions are derived from traditional prohibitions and regulations which were at first imposed through parental authority. Ultimately they are reinforced and maintained by self-controlling and self-regulating mechanisms which the person experiences as self-esteem and self-depreciation. Together these factors constitute checks upon the unlimited expression of egoistic impulses. If these checks reach a certain intensity they operate as stimuli to the anxiety mechanism. Thus the threat of business failure produces anxiety; the threat of loss of reputation, whether this be a matter of ethics or pertains to one's professional capacity, produces anxiety; threats to self-esteem produce anxiety. Dangers of this order are the final social derivatives of the earlier danger of maternal desertion, and of the later encountered danger of injury to physical integrity when parental authority and restrictions intervene.

We may finally re-state the various levels from which the stimulus to anxiety arises: The threat of complete helplessness derives from earliest infancy. The threat of separation from those to whom we have a necessary relationship stems from the dependence of the young child on the mother. The threat of physical injury originates in the value placed by the child on

his self-assertive powers. Lastly, the threat of social disapproval or of the loss of self-esteem derives from the final internalization by the child of taboos and restrictions on his egoistic strivings insofar as these violate the prerogatives of the other members of the family group.

In any given person, depending on various factors which make him finally the personality he happens to be, one or the other of these sources of anxiety will tend to predominate. All persons are capable of deriving the stimulus to anxiety from any of these sources depending on the circumstances.

III. ILLNESS AND TRAUMA AS ANXIETY STIMULI

Illness and trauma constitute frontal attacks on the basic security of the individual. Somatic self-sufficiency is impaired or destroyed; the person is forced back on the path of his emotional development to dependency on other persons. Uncertainty about the reliability of these persons may reach into the deepest levels of feeling and revive primitive anxiety tension. Because our culture emphasizes independence and self-sufficiency as prime virtues, the incapacity and helplessness produced by illness may secondarily affect the person as if he were a victim of retribution for the secret guilts which in one degree or another most people harbor. For similar reasons illness may also be looked upon as a desertion by fate, by luck, or by the particular divinity in whom the person believes. Finally, certain illness may be stigmatized as specifically revealing a person's weakness or unworthiness. Whatever the individual case may be, a quota of anxiety is added to the burden imposed by the disease or injury itself and the clinical picture is directly influenced by the anxiety and by the particular reactions of the person to it.

Before going further, it is necessary to emphasize the fact that anxiety is not merely an unfortunate complication of somatic illness. Let us assume an ideal condition of somatic illness. The patient feels somehow indisposed, recognizes there is something wrong, decides that he had better lay off for a while before he gets worse, and goes to bed. The next morning he is still sick. There is work to be done but that will have to wait. There may be really something wrong with him. He permits his wife to serve him his breakfast in bed, to tend to him, and finally to call the doctor. The diagnosis is pneumonia. The patient has confidence in his physician, follows his orders, accepts his treatment and shortly he is convalescent and back on the job.

If we consider this situation from the standpoint of our discussion we see that here the anxiety reaction to the threat of illness has been minimal but nevertheless sufficient to serve the purpose of inducing a regression to a level of organic function which established optimum conditions for recovery. The regression to passivity seen here is a flight reaction which is necessary to the survival of the sick organism. It is a sort of strategic retreat. This is a normal psycho-biological characteristic of all illness and demonstrates the adaptive rôle of anxiety.

IV. CLINICAL DEMONSTRATIONS OF ANXIETY REACTION TO ILLNESS

Returning now to the consideration of anxiety as a pathological component of somatic illness we are presented with the possibility of deviations in several directions: (A) Anxiety may eventuate in a more than necessary functional regression to passivity and dependence. (B) It may be repressed and produce secondary complicating symptoms. (C) It may lead to reactions *against* itself.

(A) *Excessive Regressive Reactions to Illness Anxiety.* In the first group the cases will run the gamut from anxious agitation about a pimple through delayed convalescence, to chronic invalidism and complete surrender.

All of us are familiar with fearful patients of the first type. These problems belong among the neuroses.

The problems of convalescence are somewhat different. As has been shown, every illness induces a certain degree of functional regression. This resumption of childlike helplessness is accompanied by a corresponding contraction of the person's interests. His world narrows down to himself and his immediate needs. He resumes the egocentricity of childhood and becomes demanding, intolerant and domineering. In part this is a means of controlling his environment despite his helplessness. In part it is a protest against the helplessness which makes him dependent. For the patient is at one and the same time grateful to those who care for him and resentful of the incapacity and insecurity which make this necessary.

During normal convalescence there is rapid reintegration of the impulse to active mastery. In cases of delayed convalescence psychic reintegration tends to lag behind somatic restoration of function. We have the clearest example of this in fracture cases in which the injured member may be mechanically useful long before the patient uses it. The developmental precursor of this situation is illustrated in the child's learning to walk. Functional capacity may be present here for some time before it is actually exploited. Some children begin to walk earlier than others not because of differences in neuro-muscular development but because of a different capacity for tolerating the anxiety which is induced by the new problem of integration. Similarly, patients will tend to cling more or less to the simpler integration which illness induces. They seem to have lost the feel of their former capacity for mastery of a more complex world than that of the sick room. The final result is determined by two variables—the severity of the illness or trauma, and the individual's tolerance for anxiety. Convalescence is thus seen to be a process which recapitulates the original problems of development and with these the original signals for anxiety.

The chronic invalidism which may follow an illness is an outgrowth of the normal problems of convalescence when these are complicated by a number of other factors. Given equal severity of illness or injury, the patient's tolerance for the anxiety-inducing problems of convalescence will

vary with his constitution, with his previous success or failure in mastering anxiety-inducing threats, and finally with the secondary gains of illness. Clinical examples will demonstrate this.

Example 1. A 19 year old male was admitted to the clinic with complaints of weakness, fatigability, vague chest pains. Two years previously he had been hospitalized for pleurisy with effusion and subsequently resided at a preventorium for six months as a tuberculosis suspect. The diagnosis was never confirmed and he was discharged in apparently good health. Since then he had remained indolently at home, felt unable to engage in any activity, was apathetic and interested only in his physical condition.

Examination was unrevealing of any somatic disease.

The social service investigation revealed that he came from a run-down family, the father an alcoholic, the mother a dull woman who submitted to the father's brutalities, and took care of a large brood of children. The family was on relief. The patient had been slow to learn to talk and walk and had left school at age 14 after completing only six grades. He had been a sickly child, had had chronic otitis media and had never been able to hold his own among seven siblings of whom he was the fourth. After leaving school he had worked sporadically as a news vendor and errand boy until he became ill with pleurisy. At the preventorium he had had a record of exemplary behavior, seemed contented and was not eager to leave.

Here we have an individual who seems never to have had enough of the wherewithal to tackle the problems of living. His chronic invalid reaction seems largely to represent a consequence of this fact.

Example 2. A 48 year old male was admitted to the hospital with a fracture of the femur and general contusions as the result of a fall from a ladder in his store. At the time of his accident he was arranging stock on the shelves. He had a delirious reaction following the application of a cast and a stormy hospital course. Two years after the injury he was a prematurely aged man, complaining of backaches and pains in his leg, unable to return to work, irascible with his wife and bitterly resigned to dependence on the bounty of a younger brother.

This patient was the oldest of three boys. For financial reasons he had been unable to continue his education beyond high school. This had been a severe disappointment. He had worked hard and helped support his family. At age 28, he had married. It had been his ambition to establish himself in business but various vicissitudes delayed this. Finally, he had succeeded only to lose his investment during the depression. Subsequently there had been years of poverty until the outbreak of the world war when he recouped his position. At the time of his accident he had been starting out for the second time in a business of his own—with this important factor operating: He was being helped to finance the venture by the next younger brother whose luck had been better.

While there are various psychic factors in this case which made it necessary for this man to injure himself and to remain ill—among them his hostile jealousy of the very brother who was helping him—it is clear that his regression to invalidism was in its comprehensive aspects a surrender to his repeated failures, despite his efforts to master the anxiety-stimuli involved in his drive for success.

Example 3. The secondary gains which are conducive to chronic invalidism generally represent opportunities to escape from life situations in

which the patient finds himself defeated or threatened by defeat. There are many complicated psychological factors operating in these cases of flight into illness which cannot be explained in the terms of the present discussion alone. However, in all of them there is the common factor of anxiety. The life situation may be characterized by actual insurmountable obstacles or by insoluble neurotic conflicts involving envy, hostility, and guilt. Whatever the case may be, the regression into invalidism serves the comprehensive purpose of protecting the person against the need of coping with the anxiety situation in its own terms.

The operation of secondary gain is well seen in the case of the constitutionally handicapped boy, cited previously. There was a specific emotional basis for his invalidism in the fact that at the preventorium he had for once in his life known what it was to be free of anxiety. To be sick really meant to him to be safe.

*Example 4.** There are patients who quite literally surrender before the impact of illness. This occurs chiefly in conditions of great seriousness. Most important and most difficult to understand is the fact that this may occur in the absence of the patient's knowledge of what exactly is wrong.

An elderly man who had sold his business preparatory to retirement to California was admitted to the hospital because of complaints of weakness, fatigue, anorexia, insomnia and cough. These symptoms had appeared after an attack of flu seven months previously. A week previously there had been an attack of pleurisy. Despite the anorexia there had been no weight loss and under observation he even gained a few pounds.

Apart from marked clubbing of the fingers the physical findings were negative. Bronchoscopy and lipiodol studies of the chest revealed nothing definite. Repeated roentgen-rays revealed widening of the superior mediastinum and an accentuation of the left hilar shadow. The roentgen-ray report stated that "early neoplastic change could not be excluded." However, the patient knew nothing of this.

Psychiatric study was requested because he had suffered from a depression 10 years previously and he was again apparently depressed. He had an attitude of complete hopelessness and appeared listless. His facial expression and bodily posture were those of apathetic surrender. He had at one time looked eagerly forward to living in California but this was now a matter of complete indifference to him. He minimized depression and emphasized his fatigue. He repeatedly stated that there must be something the matter with his chest. He had an air of anxious pleading for help but with an attitude of hopeless resignation. During office interviews, after his discharge from the hospital, he remained uncommunicative or would cry silently and murmur that he expected to die very soon.

Five months after this study, he died. In the interim weight loss had set in and weakness had become profound. Postmortem examination revealed a bronchogenic carcinoma with metastases to lymph nodes and intestines.

*Example 5.** Another case of malignant disease presented quite clearly a similar picture of passive resignation and the attitude of a hopeless plea

* I am indebted to Dr. Winston Breslin of the Division of Neuropsychiatry, Michael Reese Hospital, for the clinical histories of examples 4 and 5.

for help. A dream which this patient diffidently revealed is quite illuminating: He dreamt that he was in a house in which everything was rotting and falling to pieces.

In cases of this type illness literally delivers a knockout blow to the psychic resources of the patient.

(B). *Repression of Illness Anxiety.* Some patients do not permit themselves to become clearly aware of the specific anxiety tension which illness may induce.

Example 6. The classical example of this is the euphoria of some tuberculous patients. A striking instance is the following one: A psychiatric patient, whose mother suffered from chronic tuberculosis and was going downward, informed me that on the morning of the day that his mother died she talked with him cheerfully before his departure for school, about measuring him for a suit on which she planned to start work the following day.

We are all familiar with the euphoric megalomania of the paretic which masks the actual anxiety induced by the disintegration of his intellectual functions with increased pressure of intellectual activity and grandiose plans.

Example 7. A young man who had been diagnosed as having early syphilis appeared to take the information quite philosophically, only to report on his next visit the appearance of new symptoms: tachycardia and polyuria. Only a little exploration sufficed to reveal these to be connected with barely apprehended fantasies of an anxious type.

Example 8. A patient who had come into analysis because of a neurosis of some 10 years' standing complained also of fatigue. Two months after the analysis began it was suggested that he have a physical examination because of the excessive character of the fatigue. He was examined by a competent physician and was found to have pernicious anemia.

The psychologically important things about this case are the following: He had postponed the examination for a month after it was discussed with him, during which time he had depreciated the symptom and preferred to attach it to his neurosis. When the diagnosis was final he insisted that it was of small moment and that there was really nothing to worry about. He showed prompt symptomatic improvement under treatment and his conscious attitude towards his somatic illness continued to be one of optimism. However, his dreams began to deal with the topic of his feeling of helplessness and he began to have, while on the couch, intense recurrent visual fantasies in which he appeared as a frightened little boy at whom his father was shaking an admonishing finger. This man had good reason for feelings of guilt and of fear of loss of status, and his unconscious reaction to his somatic illness was governed by those feelings.

(C). *Flight into Health—Denial of Anxiety.* This brings us to the situation in which anxiety may lead to reactions against itself. In part, the last case described is an example of this. But there are the striking cases in which the patients are even more overt in their denial of the anxiety connected with illness.

Example 9. A man of 50 suffered from a coronary attack. Instead of following the regime advised by his doctors he pooh-poohed their caution and hastened his death by transferring his business to his bedside. This patient was one of those persons who never delegated authority. He had never been able to depend on others and in the end could not allow himself even a temporary regression into the dependency of illness.

Example 10. A male patient in his forties was admitted to the hospital for study because of loss of weight, mild anemia, and the occasional appearance of occult blood in the stools. Carcinoma of the gastrointestinal tract was suspected *but he had not been informed of this*. In the hospital he gave trouble with his complaints about the food, about the nursing service, about everything. He denied the validity of his hospitalization and insisted on going home.

During the psychiatric examination he was responsive, coöperative, apparently cheerful. He gave a coherent life story which did not reveal any unusual neurotic traits and there was no evidence of current stress in his life situation. However, there was one discrepancy. Since his admission to the hospital he had been having catastrophic dreams. Their content was vague—he only knew that they were distressingly fearsome. He continued to deny the necessity for hospitalization and finally left against advice before a diagnosis could be made.

Three weeks later he was brought back to the hospital in coma and died within 24 hours. Postmortem examination revealed a carcinoma of the stomach with metastases to the brain.

In this case the question may occur as to whether or not the patient's reaction may have been due in the first instance to the fact that he had organic disease of the brain with consequent impairment. It must be emphasized that there was no clinical evidence of an organic type of cerebral reaction at the time that he was examined, and that in any case the reaction of the patient would have encompassed this aspect of the threat to his total organic integrity.

Example 11. A chronically neurotic woman of 40 who lived in masochistic submission to a husband whom she hated, was admitted to the surgical service because of weakness, loss of weight and pain in the back which radiated into both arms. Inconstant dysphagia was present and had been interpreted as globus hystericus. In the clinic examination the only positive finding had been cholelithiasis. Because of the psychiatric history consultation was requested.

The examination revealed the old neurotic problems which had reached a pathological equilibrium. She continued to live her life as it had been at the time when she was last seen some years before. Nothing new had developed emotionally. The old hostilities and the old submissions were still in the picture. Only the somatic symptoms were new. Although she adhered to a consistent description of these new discomforts she was curiously unworried about them. Her mood was apparently good. She spoke of the old neurotic situation but without special intensity. However, while she made inquiries as to when she could go home, her attitude about this seemed tentative.

Further diagnostic procedures were advised and in the end a diffusely infiltrating squamous cell carcinoma of the esophagus was found. A month later she died in consequence of hemorrhage.

Cases of this type demonstrate the "flight into health."

V. ILLNESS ANXIETY AND THE DOCTOR AS MAGICIAN

The history of medicine begins with the history of magic. It is unnecessary to detail the facts of this. We are all aware of the attitudes of awe, fear, hope, and veneration with which patients come to a physician's office or to a hospital. The final source of such feelings is to be found in the person's anxiety of the unknown and unpredictable powers that may govern his fate. Even the most sophisticated may turn to religion and mysticism as a final support when medicine fails. The success of quackery is dependent on the survival of such primitive emotions.

The physician is often blind to the magical implications of everything about him for the patient, from his white coat to the most imposing treatment apparatus. The doctor is the embodiment of the nursing and protecting mother and of the controlling and regulating, rewarding and punishing father. Depending on the person, the will of God, of fate, or of dark powers is implicit in the doctor's presence. Whatever augments the mystery—the instruments, the techniques, the scientific jargon—augments the anxiety.

A certain amount of this is inevitable from the very nature of human beings. A great deal of it is artifact produced by the physician and his set-up. Insofar as these attitudes of patients are inevitable they are insufficiently understood and inadequately exploited in the patient's interest. Insofar as these attitudes are stimulated by the doctor they are too much disregarded or discounted.

Some patients become "experts" on their own cases as a manifestation of an intellectual effort to cope with anxiety which has been inadequately handled in rational terms by the physician. Some patients become shoppers and wind up with quacks because the physician has adhered too severely to downright rationality.

The art of medicine consists in the judicious exercise of magic and knowledge, of paternalism and maternalism. Such psychological factors as we have discussed are relevant medical data and insofar as the principles behind them are understood and consciously exploited, the art of medicine becomes a science.

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THE U. S. NAVY'S WAR RECORD WITH TETANUS TOXOID *

By W. W. HALL, F.A.C.P., Captain, Medical Corps, U. S. Navy,
Bremerton, Washington

IN ALL the wars of history, tetanus has been a major menace and a master killer. The adoption of tetanus toxoid prophylaxis by some of the military forces in World War II presented an opportunity to note the incidence of tetanus with and without active immunization and to some extent to compare success attained by different programs of immunization. Before the advent of tetanus antitoxin, "lock-jaw" attacked many of the wounded and killed almost all of its victims. Antitoxin prophylaxis and treatment improved the situation but, in spite of the best possible use of antitoxic serum, tetanus still occurred and, in those who developed the infection, the mortality remained high.

Of tetanus as a killer, Roddis¹ observes: "There is no way to number its victims, for vast numbers of them are among the infants of tropical areas of Africa and Asia where infection of the umbilical cord of the newborn is common and with almost a 100 per cent mortality. In countries where statistical information is available, the number of lives lost from tetanus before preventive measures were taken was very great. In World War I, the average rate for the German Army was 380 per 100,000 wounded with about 300 deaths per 100,000. On a basis of about 4,000,000 wounded this meant 12,000 deaths from tetanus alone."

In 1940, as the probability of war involving the United States steadily increased, serious consideration was given by the medical departments of both our Army and Navy to the tetanus problem and to the desirability of adopting universal and compulsory tetanus toxoid prophylaxis. But this would require the abandonment of serum (antitoxin) prophylaxis. Did we dare to do this? We knew from experience that though antitoxin did not afford the wounded perfect or complete protection it did hold tetanus within bounds. Could we about-face and go to war depending solely for protection against tetanus upon this relatively new agent, upon active, toxoid-developed immunity?

It had been well known, and in World War I it was demonstrated on a grand scale, that the value of antitoxin progressively decreased as the time interval between wounding and injection increased. That is, the more mobile the war, with combatants separated from base medical attention, the greater the incidence of and mortality from tetanus. In the air, on the ground, on and under the water the mechanization of war promised, for the

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Opinions expressed herein are those of the writer and do not necessarily represent the views of the Bureau of Medicine and Surgery, Navy Department.

coming strife, greater dispersion of personnel and more independent action of combatants. In this respect, in World War II, reality was to far outrun expectation in air combat and in mountain, jungle and island warfare.

The adoption of tetanus toxoid by Army and Navy followed the meeting of an unofficial conference group under the Division of Medical Sciences of the National Research Council. Representatives of the Navy, the Public Health Service, the National Research Council and the Army composed this conference group. A number of the group favored the use of plain toxoid, largely because experience with this product in France and England had been satisfactory. It was felt, too, that reactions were more apt to occur with the alum than the plain toxoid. Navy experience, however, indicated the safety of both products in man and, in a few experiments with sensitized guinea pigs, it had been demonstrated that a specimen of fluid toxoid, which contained a sensitizing protein, produced fatal anaphylaxis, while protein containing alum precipitated toxoid could be injected without reaction. We² had reported fairly extensive and very satisfactory results using alum precipitated tetanus toxoid. The largest group immunized with alum precipitated tetanus toxoid had been the midshipmen at the naval academy where all members of the academy had been so treated. Our serological examinations of these men,² and other volunteers on the U. S. S. RELIEF, where the work first began,³ in 1934, had revealed no individual who had failed to respond satisfactorily with the development of antitoxin to the injection of either fluid or alum precipitated tetanus toxoid. However, the alum toxoid had proved a much more potent antigen and had given higher serum antitoxin titers over a longer period of time. Satisfactory immunity had been developed routinely by the means of two injections of alum precipitated tetanus toxoid at one to two month intervals whereas three injections of plain toxoid at shorter intervals were required. In fact, the principle of secondary stimulation from the depot of slowly soluble alum toxoid produced a rising curve of antitoxin for about a month and reached a level, with only one injection, which probably represented a safe protective initial immunity. This seemed to be a most desirable situation to be in, when, with men by the many thousands being rushed through the training camps, clerical or technical error might cause one of the two prescribed injections to be missed.

It was, therefore, decided to adopt alum precipitated tetanus toxoid as the immunizing agent for the Navy and the Marine Corps, while the Army adopted the plain or fluid toxoid.

At first, some of our medical officers were hard to convince. Doctors are traditionally individualists and many are conservatively inclined to hold to the old method which they know to be good rather than to depend upon the new procedure which, experimental evidence and field observations notwithstanding, they feel may or may not be better. For example, one of our surgeons handling a considerable number of cases, at the time of the Pearl

Harbor attacks, refused to depend upon toxoid immunization, though service wide active immunization under Bureau directive had been completed at that time.* He gave every one of his cases antitoxin. Such attitudes soon melted away in the heat and pressure of war activity.

Table 1 gives by years the peace time strength of the Navy and Marine Corps—1919 to 1941—with the number of accidental wounds reported each year, the cases of tetanus diagnosed and the deaths. Personnel for those 23 years averaged approximately 143,000; wounds each year averaged 1400 and for the 23 years, totaled 35,840. During these years, a total of 13 cases of tetanus were reported with five deaths.

Table 2 gives average strength of the Navy by years for World War I and II with cases of tetanus and deaths and the totals of wounded for each war. In World War I, there was a total of 9,670 wounded in enemy action with two cases of tetanus and two deaths. In World War II, there were 89,988 wounded in action with four cases of tetanus and two deaths.

Examination of the medical records of the four cases of tetanus, which were verified as having been properly diagnosed as tetanus, reveals the following: All of the four were Navy personnel, no Marines having developed the infection in spite of the high percentage of Marine Corps wounded who were injured ashore in beachhead and island combat. Of the two deaths, one (designated *Case A*) died 10 days after entering the service in 1942. He reported to the training station with an infected ingrown toe nail in which

** Immunization against Tetanus in U. S. Navy.*

Requirements:

General: All personnel of the Navy and Marine Corps on active duty, regardless of age, shall be immunized against tetanus. Alum-precipitated (insoluble) toxoid shall be used.
Initial Immunization: Initial immunization shall consist of two injections of 0.5 c.c. each given intramuscularly at an interval of not less than four and not more than eight weeks. Such injections shall be given to all personnel as soon as practicable after entrance into service.

Booster Immunization: One year after the completion of the initial immunization, all personnel shall be given, intramuscularly, a single booster injection of 0.5 c.c. of alum-precipitated tetanus toxoid. Thereafter a single booster injection shall be given every four years in the event no emergency booster injections have been recorded during the interim. In addition to the above, all personnel shall receive, when possible, booster injections of 0.5 c.c. of alum-precipitated tetanus toxoid before going into combat zone, preferably one month prior to entrance into the zone.

Emergency Booster Injections: In addition to the initial and routine booster injections, emergency booster immunization, consisting of 0.5 c.c. of alum-precipitated tetanus toxoid, given intramuscularly, shall be administered immediately under the following conditions:

(a) whenever an individual receives a wound or severe burn in battle, (b) whenever a patient undergoes a secondary operation or open manipulation, if, in the opinion of the medical officer, there exists the possibility of contamination with tetanus spores or organisms, and (c) whenever an individual receives punctured or lacerated non-battle wounds, powder burns, or other conditions which might be complicated by the introduction of tetanus spores or bacilli.

Precautions: When administering tetanus toxoid, especial care shall be exercised (1) to assure that the injections are deep and given intramuscularly; and (2) to avoid injecting tetanus toxoid directly into the blood stream. The preferred site of injection is the deltoid muscle, approximately half the distance from the point of the shoulder to the insertion of this muscle. Due consideration shall be given to the possibility of a sensitivity reaction.

TABLE I
Tetanus Cases and Deaths
1919-1941
U. S. Navy *

Year	Average Strength	Cases	Deaths	Total Wounds (Cases)
1919	298,774	3	2	2,850
1920	140,773	0	0	1,552
1921	148,861	2	1	1,574
1922	122,126	0	0	1,384
1923	116,565	0	0	1,308
1924	119,280	3	2	1,274
1925	115,391	1	0	1,407
1926	113,756	0	0	1,413
1927	115,316	0	0	1,438
1928	116,047	0	0	1,332
1929	117,388	0	0	1,391
1930	117,453	1	0	1,489
1931	112,767	1	0	1,444
1932	110,717	1	0	1,461
1933	108,183	0	0	1,442
1934	109,383	0	0	1,438
1935	114,188	1	0	1,423
1936	124,408	0	0	1,420
1937	132,855	0	0	1,484
1938	139,216	0	0	1,316
1939	149,618	0	0	1,331
1940	202,614	0	0	1,704
1941	348,926	0	0	2,965
Total		13	5	35,840

* Includes Marine Corps—Source: Surgeon General's Annual Reports.

TABLE II
Tetanus—U. S. Navy *
World War I and World War II by years

Year	Average Strength	Total Cases	Deaths	Total Admissions for Wounds
1917	245,580	0	0	} World War I 9,670**
1918	503,792	2	2	
Total		2	2	
1942	834,639	2(A)(C)	1(A)	} World War II 89,988**
1943	2,108,379	1(B)	1(B)	
1944	3,349,798	0	0	
1945	3,673,855	1(D)	0	
Total		4	2	

(A) Existed prior to enlistment.

(B) Immunization record incomplete and unsigned, probably received neither basic nor booster injections.

(C) Received basic immunization but no booster injection.

(D) Fully immunized.

* Includes Marine Corps—Source: Surgeon General's Annual Reports.

** Include only wounds resulting from enemy action.

See footnote on page 302.

tetanus developed; he was given a total of 200,000 units of tetanus antitoxin. He died two days after the disease was recognized, 10 days after entering the service. Tissue was removed from the infected toe and tetanus bacteriologically verified. This case was recorded as having contracted his infection prior to enlistment (EPTE) and was not considered as a failure of toxoid immunization. *Case B*, who developed tetanus and died in 1943, sustained a compound fracture of the leg when he fell from a window. Tetanus was recognized clinically seven days after the accident. Large amounts of tetanus antitoxin were given but the patient became rapidly worse and died in a few days. Examination of his immunization record revealed an incomplete entry of two injections of alum-precipitated tetanus toxoid earlier in the year, not signed by the medical officer. At the time of injury, booster injection was noted as "ordered" but not recorded as having been given. This case was not accepted as tetanus in an immunized individual, there being doubt that he received any toxoid at all, basic or booster. *Case C* developed tetanus in 1942 after he had sustained a crushing injury of the legs and feet. Gangrene resulted with later amputation of left leg and toes of right foot. Tetanus developed in a mild or chronic form about one month after injury. The disease was successfully treated with tetanus antitoxin. Immunization record indicated that he had received two basic injections of alum precipitated tetanus toxoid but that he had not received a booster injection of toxoid when injured nor at any time subsequently. Time of onset and course of the tetanus infection suggest partial protection from the original immunization. Because no booster injection was given, this case is not accepted as a failure in a fully immunized case. *Case D* was admitted in 1945 with a crush injury left great toe. Symptoms of tetanus developed eight days later, with recovery in 10 days under antitoxin therapy. Immunization record in this case indicated that the two basic immunizing injections had been given in 1943, an annual booster injection in 1944 and a booster injection given after injury. Clearly, this was a case in which active immunization failed fully to protect. The mildness of the infection and rapid recovery may possibly be accepted as indicating partial protection. Summarizing the above, we have one nonfatal case of tetanus in a fully immunized man; one nonfatal case of tetanus in a man who had received the basic immunization but not the emergency booster injection; one fatal case of tetanus in a man who had received no immunization and one fatal case of tetanus in a man whose record is incomplete and who probably received no toxoid. It is worthy of note that none of these four cases were combat casualties.*

* (1) The U. S. Navy Surgeon General's annual report of 1943 lists cases of tetanus as 7. This error was discovered too late for correction and was due to the statistical tabulation of cases of "trismus," resulting from molar tooth extraction, as tetanus. The USPHS Manual is used in coding for illness. The Statistical Division Editor, using this as a guide, placed trismus under the diagnosis number of tetanus. (2) *Case B*, though occurring in 1943, is not listed in this annual report as a death due to tetanus since the report provides only the principal or primary cause of death. According to "Joint Causes of Death" case B is recorded—Cause of Death, Primary: Fracture Compound; Cause of Death, Secondary: Tetanus.

Reactions experienced in the use of alum precipitated tetanus toxoid have been minor in nature and relatively very few in number. When precautions regarding placement of the injection intramuscularly in the center of the deltoid have been followed, skin irritation has been avoided and only minor soreness of the muscle has been the rule. Alum precipitated tetanus toxoid has proved to be a most safe and satisfactory immunizing agent.

In theory, there are at least three reasons for possible failure of active immunization fully to protect against tetanus. The first is the inability or failure of the individual's immune mechanism to react. That such failure does occur in various immune processes has been demonstrated by animal and human experimental observations and in the clinical field. That such failure to react to properly administered alum precipitated tetanus toxoid is a very rare occurrence seems to be demonstrated by our experimental serological results² in which no individual failed to react with a titratable antitoxin response to basic immunization or to react with a prompt rise in titer to a booster or challenge dose of toxoid, even though the booster was given when the circulating antitoxin had fallen to a hardly detectable level two years or more after original injection. Such field experience as reported above, where tetanus was almost eliminated, serves even more clearly to indicate a highly uniform and reliable response. "The proof of the pudding is in the eating." The second reason for possible failure is sudden flooding of the body with high potency toxin from a massive and virulent infection. A third reason for failure might be suppression of an immune response to a challenge dose of toxoid or toxin. Toxemia or severe malnutrition might conceivably operate in this manner even though the original immune response had been satisfactory.

Some effort has been made to establish an arbitrary serum antitoxin level⁴ which could be considered a safe protective level. Undoubtedly of greater importance is the ability of the individual's immune mechanism promptly to respond to toxoid or toxin stimulation.

In the discussions of tetanus during World War I and World War II,⁵ it has frequently been emphasized that in a highly fertilized farming area, where herbivorous animal excreta laden with the spores of *Cl. tetani* enriches the ground, combat is followed by more tetanus from soil contamination of wounds than warfare in nonarable regions. The unsavory records of World War II tetanus, in the German troops fighting in Europe, and of the Japanese forces engaged in Pacific island warfare, demonstrate the fact that tetanus spores were everywhere that our men fought and that freedom from tetanus depended upon immunity and not upon lack of infecting organisms.

A vignette of tetanus among the Japanese casualties was given in 1944 by Comdr. H. J. Cokely, (MC) USN,⁶ as follows: "During a recent evacuation of patients by this vessel from the combat zone, we embarked 284 Japanese wounded. We found them to be generally dirty, emaciated and with wounds that had been improperly treated. This, no doubt, was due to the

nature of the campaign. The main point of interest, however, was the presence of a large number of cases presenting symptoms of tetanus.

"I would consider a more formal report of the course, treatment and results in these cases had adequate records been kept. This was impossible owing to the large census on that particular trip with the resultant overload on personnel.

"From what we can gather, the Japanese troops are not routinely immunized against tetanus on their induction into service. Such immunization is reserved as a procedure to be carried out on their arrival in the combat area. As a result, many of their troops do not receive the benefit of this valuable measure.

"The incidence of symptoms of tetanus in Japanese wounded was 4.93 per cent. The mortality rate of those with tetanus during the period that they were on this vessel was 71.43 per cent.

"Faced with this large number of cases of tetanus, we found our supply of tetanus antitoxin inadequate. It was, however, spread around and utilized in those cases where the outlook appeared favorable. Having a plentiful supply of penicillin aboard, each case received 25,000 units intramuscularly every three hours. This seemed beneficial in some cases while in others the clinical picture progressed from trismus to generalized spasms, opisthotonos and death. Some, who were alive when transferred from the ship, were in none too good condition.

"For a control we had at that time 384 wounded of our forces aboard. These troops were engaged and wounded in the same area as were the Japanese. All of our casualties had been immunized against tetanus and had in the main received booster injections of the toxoid prior to action. They had, without exception, received an additional 0.5 c.c. of tetanus toxoid following their injury. There was no incidence of tetanus in our troops.

"To me this is a very valuable lesson and direct evidence of the efficacy of immunization against tetanus and will be of interest to those medical officers who, day after day, week in and week out, immunize the many thousands of our military personnel. Certainly this widespread program of protection against tetanus is now paying dividends."

Roddis¹ reports: "In the attack on Saipan an opportunity was afforded of seeing the contrast between Japanese wounded of the Imperial Army who had received tetanus toxoid and members of labor groups largely unvaccinated. Among the latter there were nearly .15 per cent of deaths from tetanus and not one from the former. Apply such a death rate to hundreds of thousands of wounded and one gets a graphic picture of the lives saved by the use of tetanus toxoid as an immunizing agent."

Tetanus in the German forces has not been officially reported and perhaps will not be. However, numerous U. S. Army and Navy Medical Officers have reported that tetanus was rife among the German wounded in their hospitals and in the wounded prisoners in ours and that the mortality was

high.^{7,8} Information gleaned by Alvis⁹ while attached to the Naval Technical Unit Europe indicated that only the paratroopers of the Luftwaffe were routinely immunized. The paratroopers were given active immunization because it was believed that they might not have medical attention readily accessible so that passive immunization could be given promptly. It is reported that only four cases of tetanus developed with one death in the combined paratroop activities.

The record of protection against tetanus in the British forces is a mixed one. Not all of the troops under the British flag were actively immunized and in some of those immunized the protection was not considered satisfactory by the medical authorities, due to the fact that early in the war numbers of men had to be let go with but two injections of fluid toxoid when a standard course was determined as three injections. Boyd⁵ reports 22 cases of tetanus in the British forces among those actively immunized, with 11 deaths, a 50 per cent mortality. Eleven of these 22 cases had also received prophylactic antitetanic serum (ATS), while 11 cases had not received ATS. The deaths in the group receiving ATS as well as toxoid immunization were 2 or 18.2 per cent mortality and in that group which had only active immunization the deaths were 9 or 87.8 per cent mortality. Additional figures in cases not actively immunized are given as follows: Not actively immunized but given prophylactic ATS—23 cases, 10 deaths, mortality 43.8 per cent; not actively immunized, no prophylactic ATS—39 cases, 19 deaths, mortality 48.7 per cent. Further, there were 18 cases of tetanus in which active immunization was incomplete or doubtful, three of these received prophylactic ATS and two died, a mortality of 66.6 per cent while 15 received no ATS, prophylactically with five deaths, a mortality of 33.3 per cent.

Boyd⁵ feels that the failures in active immunization, 22 cases, may be attributed to "(a) Massive infection in which the amount of the toxin secreted overwhelms the blood antibody level produced by active immunization: (b) to a defective response to active immunization resulting in an antitoxin level below that required to neutralise the average infection—out of 22 cases, the failure in 6 may be attributable to the former cause. In the other 14, however, lack of protection could be explained only by the existence of an inadequate level of preformed antitoxin. To meet with such cases, the Canadian and U. S. Army Medical Officers give to each wounded soldier 1 c.c.-toxoid so as to stimulate early antitoxin production. The British Army Medical Officers prefer to give a single dose of 3000 units antitoxin in order to increase immediately the antitoxic content of the blood above the critical level." Boyd recommends the latter procedure as he feels it affords protection to poor or non-reactors to active immunization.

In comparing the mortality in the completely and incompletely toxoid immunized British, who also received antitetanic serum, with the mortality in those actively immunized, who had not received ATS, and further comparing these mortality figures with the mortality in nonimmunized cases who

had or had not received prophylactic ATS, it should be remembered that large numbers are required to balance the effect of unknown variables such as virulence of infection, nature and size of wound and to render the results statistically highly significant. However, on a purely theoretical basis it has seemed to us that the presence of ample exogenous antitoxin might prevent toxin, produced in an infected wound, from stimulating endogenous antitoxin production. That is, antagonism rather than synergism may result and the active process for the time being be suppressed. Where fluid or plain toxoid is used, the antitoxin probably persists in the tissues longer than does the toxoid. Alum precipitated toxoid, on the other hand, is released more slowly, has been demonstrated³ to produce a rising curve of antitoxin in the blood for at least a month and presumably would outlast simultaneously injected antitoxin which disappears steadily after injection and is completely gone from the body in about two weeks.

Reports on the incidence of tetanus in the Canadian Forces where fluid or plain toxoid was used, three injections to the basic course with injury booster injection, are not now available. Unofficial information indicates that their results were quite satisfactory.

Tetanus toxoid was also used in the French, the Italian and in the Russian troops. Information on the program of injection in these forces and on their results is not now available.

In regard to tetanus in the U. S. Army in World War II, Major General Norman T. Kirk, Surgeon General reporting on the "Health of the Army"¹¹ says: "The record for the prevention of tetanus was especially remarkable. In spite of the many thousands of battle wounds in which tetanus has always been feared as a deadly complication, there were only five (5) deaths from tetanus during the entire war, and only two (2) of these were in soldiers who had been properly immunized." Total cases of tetanus in the Army¹² are reported as twelve (12). Analysis of the immunization status indicates that four (4) of these, two fatal and two nonfatal, had received complete immunization (basic immunization and emergency stimulating injections). Two cases, one fatal and one nonfatal, had received the basic immunization but had not received the emergency stimulating injection. Six cases, two fatal and four nonfatal, had received no immunization.

SUMMARY

1. The use of alum precipitated tetanus toxoid in immunization of Navy and Marine Corps personnel during World War II resulted in the almost complete elimination of tetanus.

2. No combat casualties developed tetanus. However, tetanus developed in four cases of accidental injury.

3. One nonfatal case (Case D), fully toxoid immunized, developed tetanus; recovered in 10 days under antitoxin.

4. One fatal case (Case A) had no immunization; entered the service with the infection and died in 10 days.

5. One fatal case (Case B) probably received no immunization. Immunization record incomplete.

6. One nonfatal case (Case C) who had received basic immunization but no emergency booster injection developed mild tetanus one month after injury.

7. Tetanus with high mortality occurred in nonimmunized German and Japanese at the same terrific rate that the history of tetanus in previous wars had taught us to expect.

8. The British record, reported by Boyd,⁵ using antitoxin prophylactically at the time of injury, in men previously toxoid immunized, is quoted. We believe that antitetanic serum given prophylactically in the actively immunized presents no advantage. In fact, it seems that when fluid toxoid is used antagonism rather than synergism between the two protective mechanisms may result during the entire time that toxoid is present in the body and the process of formation of endogenous antitoxin may be suppressed by the presence of the exogenous antibodies.

9. The excellent record of the U. S. Army using plain or fluid toxoid is quoted.

CONCLUSIONS

1. Complete dependence upon active immunization alone for protection against tetanus is fully justified.

2. Both plain and alum precipitated tetanus toxoids are excellent antigens. Alum precipitated tetanus toxoid is preferred because (a) a higher level of antitoxin response results from the alum precipitated toxoid, and (b) two injections of the alum precipitated toxoid are ample for satisfactory immunization while three of the fluid toxoid are required.

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RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE OF RECENT YEARS

(Ninth Rheumatism Review) *

Part II

By PHILIP S. HENCH, M.D., F.A.C.P., *Rochester, Minnesota*
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WALLACE GRAHAM, M.D., F.R.C.P.(C), *Toronto*,
W. PAUL HOLBROOK, M.D., F.A.C.P., *Tucson, Arizona*,
L. MAXWELL LOCKIE, M.D., F.A.C.P., *Buffalo, New York*,
CURRIER MCEWEN, M.D., F.A.C.P., *New York City*,
EDWARD F. ROSENBERG, M.D., F.A.C.P., *Chicago*,
ROBERT M. STECHER, M.D., F.A.C.P., *Cleveland*

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ALKAPTONURIA; OCHRONOSIS; OCHRONOTIC ARTHRITIS (OSTEOARTHRITIS ALKAPTONURIA)

ALKAPTONURIA represents the presence in urine of alkapton bodies, aromatic compounds which on oxidation or the addition of certain chemicals produce dark urine. The alkapton bodies consist of (1) homogentisic acid, the most common, (2) melanin, less common, or (3) aromatic compounds related to the external use of phenol—not encountered since 1933. Alkaptonuria may produce no symptoms or signs but in severe or long-standing cases the presence of the alkapton bodies in circulating blood may produce ochronosis—pigmentation of certain bodily tissues chiefly cartilages of ears, nose and joints, sclerae, cornea and sometimes skin. Ochronosis in turn may be symptomless but in time the ochronotic deposits in joint cartilages produce extensive degeneration which may result in a special form of arthritis—"ochronotic or alkaptonuric osteoarthritis."

Clinical Data. Alkaptonuria is relatively rare; about 200 cases have been reported to date.^{1640, 1761} Ochronosis is even more rare: 82 cases had been collected up to 1942.^{871, 1640} Eleven new cases of alkaptonuria (seven with ochronosis; nine with arthritis) were reported.^{3, 409, 836, 1080, 1399, 1640, 1761, 1982} Homogentisic acid was present in five cases; both homogentisic acid and melanin in one case.¹⁷⁶¹ In the remaining five cases the alkapton bodies were not identified. "Ocular ochronosis," pigmentation of sclerae or cornea, was present in seven of the 11 cases. An excellent review of ocular ochronosis, with an extensive review of the literature and excellent color plates, was made by Smith.¹⁶⁴⁰

Ochronosis and arthritis were absent in two alkaptonuric children (Abbott, Mandeville and Rein³). Ochronotic arthritis was present in the other nine new cases of alkaptonuria. Joints most often affected were spine, shoulders, knees, hips. Ochronotic arthritis objectively and clinically resembles somewhat rheumatoid arthritis but roentgenographically it resembles osteoarthritis, but of a special and rather characteristic type. The arthritis is chronic with occasional acute exacerbations and synovial effusions. Certain of the new cases were of special interest: the first case of ochronosis with prostatic calculi removed surgically was reported by Young¹⁹⁸²; homogentisic acid was found in urine and in synovial fluid. The first case in which both homogentisic acid and melanuria were noted was reported by Swirsky.¹⁷⁶¹ In this case there appeared to be a definite chemical relationship between the articular symptoms and the amounts of homogentisic acid in urine: when disease in the joints flared up, the urinary acid seemed to be increased. The first case of alkaptonuria with hyperuricemia was reported by Leslie: in this patient, a woman 24 years old, visible ochronosis was absent but severe arthritis was present. It was chronic with acute exacerbations incompletely relieved by colchicine. Gout was presumably not present. Strangely, when colchicine was given the blood uric acid rose from 8.6 and 7.9 to 13.3 mg. per 100 c.c., "probably because of mobilization."

[Colchicine does not mobilize uric acid. Could the metabolic abnormalities present in this case have produced a false color reaction for uric acid? It would be interesting to apply the uricase method in this case.—Ed.]

Roentgenograms. Roentgenographic features are unusual and in spine so characteristic as to be almost pathognomonic. They consist of marked thinning and calcification of intervertebral disks sometimes with exostoses or ligamentous calcification. Affected shoulders reveal unusual thinning of articular space and large exostoses.^{836, 1399}

[One of us, P. S. H., has seen three cases; the spinal roentgenograms were so striking and individualistic that he would agree with others¹³⁹⁹ that to one aware of the roentgenographic picture, the diagnosis of ochronotic spondylitis could be made or at least strongly suspected, on this basis alone.—Ed.]

Laboratory Data. A method for the instantaneous diagnosis of alkaptonuria on a single drop of urine was reported^{560, 684}; a drop of alkalinized urine placed on regular sensitized photographic paper instantly turns the paper black.

Pathology. Ochronotic cartilage was described on biopsy of one joint (Hertzberg⁸³⁶).

Etiology and Pathogenesis. Theories were reviewed.^{1080, 1399, 1640, 1761} No new ideas were offered. Presumably the amino acids, tyrosine and phenylalanine, are metabolized normally to produce homogentisic acid which, in cases of alkaptonuria, is not metabolized further but appears in blood and urine instead of being acted on by an enzyme or catalyst to produce acetone as in normal persons. Presumably patients who have alkaptonuria lack an essential enzyme. Ochronosis develops in about 50 per cent of cases of alkaptonuria and in most cases ochronotic arthritis develops in time.¹³⁹⁹

[Seeing such cases in which a pigmenting "irritant" hastens cartilage degeneration resulting in a special osteoarthritis, one wonders whether the analogy could be applied to primary osteoarthritis in which a nonpigmenting chemical irritant might be operating rather than a simple mechanism of ordinary wear and tear.—Ed.]

Treatment. Various methods, mostly of uncertain merit, were discussed (Leslie¹⁰⁸⁰): liver extract, ascorbic acid, vitamins C and E. Use of salicylates or aminopyrine decreased urinary homogentisic acid and relieved articular symptoms in one case (Swirsky¹⁷⁶¹).

GAUCHER'S DISEASE AFFECTING BONES AND JOINTS

This rare familial disorder of lipid metabolism is characterized by deposition of kersin in reticular cells of the reticuloendothelial system. Infiltration of bony trabeculae by Gaucher's cells eventually produces mottling as seen in roentgenograms. Involvement of femoral heads may produce osteoarthritic lesions suggesting Legg-Calvé-Perthes' disease; to 16 such cases previously reported in the literature eight cases were added (Schein and Arkin). In one case the disease began as an "arthritis" of many joints of a child. Diagnosis was made after puncture of sternal bone marrow.

Another case presented unusual features which included scattered ecchymoses, recurrent migratory polyarthritis "not unlike rheumatic fever," spindling of finger joints, narrowing of articular spaces in roentgenograms, osseous abnormalities including multiple cystic changes especially in femoral heads. Biopsy of humerus revealed Gaucher's cells (Reed and Sosman).

PSORIATIC ARTHRITIS

Incidence. It is generally agreed that the association of arthritis of the rheumatoid type with psoriasis is significant and not merely the coincidental occurrence of two rather common diseases. Psoriasis was present in 2.7 per cent of 300 unselected patients with rheumatoid arthritis, in only 0.7 per cent

of a similar number of nonarthritic controls.⁹⁰ The incidence of arthritis "of one form or another" in cases of psoriasis was reported as 12¹³¹⁵ and 15 per cent.²³² The incidence of "arthritis" among psoriatics varied from 0.2 to 25 per cent according to others.⁸⁹⁶

Clinical Data. Exacerbations and remissions of joint manifestations synchronous with those of nails were again noted.^{90, 1402} Diagnostic emphasis was placed on the involvement of terminal phalangeal joints in association with nail lesions. But arthritis confined to the terminal joints alone is not common in psoriasis and was seen in only three of 26 cases of chronic arthritis and psoriasis.⁹⁰ The remaining 23 patients had arthritis of the rheumatoid type, 17 had psoriatic nail changes of which 13 had terminal joint involvement. Bauer, Bennett and Zeller⁹⁰ preferred to restrict the term "psoriatic arthritis" to cases in which the arthritis is limited to the terminal phalangeal joints, but involvement of these joints may occur in rheumatoid arthritis.⁹⁰

[Uncommonly.—Ed.]

Three cases of psoriatic arthritis were reported by Franks and Wallace: in two the psoriasis antedated the arthritis which appeared with a flare-up of the skin lesion. In one case the skin and articular lesions appeared almost simultaneously, the arthritis being noted "a short time" before penile psoriasis. Joints affected were fingers and feet (but not terminal joints), knees and sternoclavicular joints, giving the appearance of rheumatoid arthritis. Under treatment the joints improved "correspondingly to the improvement made by the skin" even though in one case treatment was confined to skin.

Although in most of their 26 cases of chronic arthritis with psoriasis the condition seemed to Bauer, Bennett and Zeller to resemble rheumatoid arthritis, despite the involvement of terminal phalangeal joints in 17, one of their cases was unique. A man, aged 68 years, began to have arthritis of the terminal phalangeal joints with nail changes at age 24 years. Psoriasis of scalp and umbilicus occurred at age 39 years. Terminal joints were swollen and fingers and toes had shortened. After death from coronary occlusion examination of terminal joints revealed "unusual and distinctive alterations" (marked articular destruction and bone resorption) because of which Bauer, Bennett and Zeller concluded that in rare cases "articular lesions are sufficiently unlike those of rheumatoid arthritis to suggest important differences in pathogenesis if not in etiology." Even so they admitted that such an unfamiliar joint lesion might represent a rare form of rheumatoid arthritis.

An even more unique case was reported by Jungmann and Stern as "a possible example of arthritis psoriatica." A woman, aged 51 years, had had chronic polyarthritis for 18 years; psoriasis had commenced "simultaneously with her joint trouble." Hands and fingers were childlike, rubbery and hypermobile. Hips and knees were flexed. Roentgenograms showed remarkable changes: partial or complete dissolution of certain carpals, metacarpals, phalanges, humeral heads; tapering of ulnae, metacarpals, clavicles, metatarsals; destruction and dislocation of sternoclavicular, acromioclavicular and shoulder joints; fusion of radiocarpal joint and certain vertebrae.

Pathology. The pathologic changes in the joints of six patients with arthritis and psoriasis, four of whom had involvement of terminal joints, were indistinguishable from those of uncomplicated rheumatoid arthritis.⁹⁰ But a striking difference was found in the one psoriatic patient (noted above) with arthritis confined to the terminal phalangeal joints of both fingers and toes. Marked

articular destruction and resorption of bone caused pronounced shortening of the middle phalanges. Pronounced marginal overgrowth of bone at the sites of tendon insertions in the distal phalanges had led to the formation of cuplike deformities. The diffuse osseous atrophy usually seen in rheumatoid arthritis was not present. Most of the terminal joint spaces were replaced by dense acellular fibrous tissue in which inflammatory changes were absent or minimal.

The histopathologic findings in the skin in 225 cases were reported (Burks and Montgomery).

Etiology. 1. Of the Arthritis. Two views continue to prevail: (1) that the skin lesions produce a toxin which affects joints, hence the skin disease is the cause of the arthritis (relief of joints by treating skin supports this view); (2) that both skin and joint lesions result from some agent acting on the two different organic systems and are therefore coördinated (the occasional appearance of the arthritis before the skin lesion supports this view). The first view was favored by Franks and Wallace, the second by Jungmann and Stern who suspected that psoriatic arthropathy as seen in their case might be related to that seen in "main en lorgnette" (Weigeldt, 1929^{1d-r}).

2. Of the Skin Lesion. A strong family history among psoriatic patients was again noted.^{666, 844} The disease is very rare among Negroes.¹⁵⁴³ Evidence was presented in support of an infective etiology.⁸⁴⁴

Treatment. 1. Of Joints. In one case the joints cleared up apparently as a result of treatment to the skin lesions; in two other cases additional treatment for joints (physical therapy) was used.⁵⁸⁹ In four of nine cases with psoriatic nails roentgen treatment of nails produced complete symptomatic relief of arthritis of adjacent terminal joints and in four, marked improvement.¹⁴⁰²

2. Of Nails. Popp and Addington¹⁴⁰² advocated roentgen therapy for psoriatic nails and arthritis of adjacent terminal joints. Radiation was applied to the dorsum of the hands or feet from the tip of the nail to the wrists or ankles. Complete remissions occurred in the nails with, as yet, no exacerbations in six of 24 cases, and marked improvement in 10 others. The results lasted from six months to as long as five years. But Saunders¹⁵³⁹ noted disappointing results.

3. Of Skin. Goeckerman's regimen (1933^{1a}) was favored by several.^{232, 589, 1315} Other regimens were outlined.^{143, 163} Results with vitamin D were conflicting.^{1032, 1539, 1966} Citrin lemonade which contained vitamin P and ascorbic acid was recommended by some⁶⁶⁶ but others noted no benefit from ascorbic acid, adrenocortical extract, a low potassium diet,¹⁰⁹¹ or deproteinized pancreatic extract (depropanex).⁴⁸² The blood lipid content was unaffected by use of lipocaic.^{163, 1866} "Routine treatment" plus the use of soy bean-lecithin mixtures seemed to help in 15 "very resistant" cases⁶⁶⁹ and was recommended.^{710, 1626}

"OPERA-GLASS HAND" (LA MAIN EN LORGNETTE)

The fourth case of this rare condition was reported by Crain⁴⁰³ in a man, aged 55 years, who had had what was apparently chronic polyarticular rheumatoid arthritis with severe acute exacerbations for 13 years.

Features included: short stubby fingers, skin over finger joints wrinkled and folded, no ankylosis of phalangeal joints, extensive osteoporosis, resorption and partial dissolution of joints of fingers, wrists, elbows, shoulders, hips resulting in "false joints"

and "a telescopic type of subluxation." These changes in hips produced the appearance of "Otto pelvis."

The conditions presumably represented "rheumatoid arthritis engrafted upon or followed by some other disease such as hyperparathyroidism with alteration of the arthritis as is the case in psoriatic arthritis." In the original description by Marie and Leri (1913) necropsy studies revealed extensive fatty degeneration; bones were reduced to mere shells and there was no evidence of cellular activity of a reparative or destructive nature. Because joints other than hands were affected Crain⁴⁰³ suggested the term "generalized absorptive arthritis." The case resembled that of Nelson (1938).¹¹

[Unfortunately no photographs of joints were included. The roentgenographic features in this case were somewhat like those in a case of hyperparathyroidism noted by Gutman, Swenson and Parsons (1934),^{1b} even more like those in the cases of psoriatic arthropathy described by Jungmann and Stern, and by Schlionsky and Blake (1936).^{1d} In the unique case of chronic polyarthritis with psoriasis described by Bauer, Bennett and Zeller⁹⁰ the dissolution of articular structures was associated with dense acellular fibrous tissue; no fatty degeneration of bone was noted. Similar roentgenographic features were present in Vishnevsky's cases of "deforming xanthomatous rheumatism, a new form of chronic rheumatism." Possibly there exists a pathogenetic relationship between these four conditions: "opera-glass hand" (without psoriasis), psoriatic arthropathy, the arthropathy of xanthomatous rheumatism, and that of hyperparathyroidism.—Ed.]

HEMOPHILIC ARTHRITIS

Sixteen cases were noted, one by Balensweig⁶⁶ and 15 by McDonald and Lozner who discussed the roentgenographic changes and their value in differential diagnosis.

Roentgenographic changes occurred in one or both knees of all, in one or both elbows in 14 of 15 cases.¹¹⁹³ In general the involvement increased with age and ranged from mild changes (slightly increased periarticular density, marginal spurs) to severe changes (narrowing and irregularity of joint space with marked subchondral cyst formation). Roentgenographically acute hemophilic arthritis simulates any synovitis with distention of articular space. But chronic hemophilic arthritis is somewhat distinct roentgenographically: cystic changes are more frequent and severe in hemophilic than in rheumatoid or osteoarthritis. Tuberculous arthritis is less easy to differentiate.¹¹⁹⁴ In Balensweig's case⁶⁶ diagnosis was based on the roentgenographic appearance, marked irregularity of tibial and femoral articular areas, cystic degeneration within femoral and tibial condyles.

Laboratory diagnosis of hemophilia was discussed.¹⁴²² Coagulation time was decreased by lyophil human plasma,⁹¹⁸ rabbit thrombin given orally¹⁷⁶³ or human globulin given intravenously or intramuscularly.¹²⁴⁸

"ALLERGIC ARTHRITIS"

A factor of allergy (bacterial, food, other) is suspected by some to operate in the production of several diseases which affect joints, in particular rheumatic fever, rheumatoid, tuberculous and gouty arthritis and palindromic rheumatism as noted in the appropriate sections of this review. Serum sickness and the occasional synovial reactions to sulfonamides or penicillin might, in the broader sense, be listed under the heading "allergic arthritis," but will be discussed under "Pharmaceutic Arthritis and Arthralgia." The average reader thinks of "allergic arthritis" in a narrower sense to mean an acute or subacute (possibly

a somewhat chronic) arthritis caused by a specific food or other antigen which acts like pollen to the hypersensitive. Presumably in such cases the administration of the offending antigen would provoke an articular reaction every time and the permanent removal of the antigen would allow the arthritis to disappear. Rare indeed have been the case reports truly indicative of such a type of allergic arthritis.^{1d}

Turnbull¹⁸²³ again reported his belief that food allergy is a factor in many cases of "arthritis" but that in individual cases the hypersensitivity changes from year to year; the arthritic patients become immune to antigens to which they were formerly sensitive but become sensitive to others. He reported 10 cases of chronic arthritis of three months' to 10 years' duration, mostly in elderly women. When foods, to which skin tests showed them to be sensitive, were avoided, complete relief of symptoms occurred and lasted from 13 to 100 months until the patient's sensitivity changed. Sensitivity to other foods having then occurred, the arthritis returned but was again controlled by avoiding foods to which new skin tests showed new sensitivity.

[The clinical types of arthritis present were not described; the cases were just called "arthritis." The clinical descriptions were brief; no roentgenograms or photographs were shown; no laboratory data were given except on skin tests. Rheumatoid arthritis may have been present in some, osteoarthritis in others. Except for the occasional mention of return of symptoms when patients broke rules and ate the interdicted foods, no controlled provocative tests were done. The author surely knows that his views expressed since 1924, have received scant acceptance. But more convincing, appropriate evidence, such as controlled provocative tests with "before and after photography" of joints, would be viewed sympathetically.—Ed.]

Skin tests with foods were given 25 patients with "subacute or chronic rheumatism" by Vaughan.¹⁸⁴⁹ No connection between positive skin reactions and rheumatic flare-ups was found. Dietary restrictions based on skin reactions had no effect.

Having searched inconclusively for allergy in rheumatic patients, Vaughan¹⁸⁴⁹ searched for "arthritis" in 1,000 allergic persons with hay fever, urticaria, angio-neurotic edema, migraine, gastrointestinal allergy or allergic dermatitis. About 20 per cent complained of "rheumatic pains, past or present": of these 206 patients 90 showed "joint pathology," 116 did not. Of the former, nine had rheumatoid arthritis, 32 osteoarthritis, 29 "combined arthritis," two traumatic and 18 unclassified arthritis. Of the 1,000 patients 27 "found that certain specified foods produced exacerbation or recurrence of rheumatic symptoms": joints were objectively negative between attacks in some, not in others. In these 27 cases the arthritis was classified thus: intermittent hydrarthrosis in four; intermittent hydrarthrosis with chronic arthritis in one; subacute rheumatoid arthritis in three; osteoarthritis in three; chronic arthritis [probably osteoarthritis—Ed.] in eight; joints objectively negative in six; joints not examined in two. One patient with recurrent attacks provoked several attacks with strawberries or raspberries although skin tests to strawberries were negative. An elderly woman with chronic "combined arthritis" noted articular flare-ups whenever she ate chocolate. When she did not eat eggs, the garden work caused "little or no discomfort"; when she did eat eggs, the trauma of this work caused "subacute flare-ups in the fingers."

Vaughan¹⁸⁴⁹ considered skin tests with food extracts unreliable; food diaries were required in half the cases to uncover the offending food. He concluded: about half of these 27 cases "appear to belong in the group which Hench and Rosenberg⁸¹⁸ term 'palindromic rheumatism.' It would appear that food or

inhalant allergens may be a cause of palindromic rheumatism. It does not follow that it is the only cause."

[It has not been proved that food or inhalant allergens are the cause of palindromic rheumatism.—Ed.]

INTERMITTENT HYDRARTHROSIS

In most cases "intermittent hydrarthrosis" represents rheumatoid arthritis according to Ropes.¹⁴⁹³ In four of her five cases it occurred at the onset or during the course of rheumatoid arthritis and the cases "resembled in all respects those of idiopathic hydrarthrosis characterized by *periodic* swelling recurring at regular intervals with great precision." In one case of idiopathic hydrarthrosis of knees for 20 years, an elevated sedimentation rate, aching in other joints, and synovial thickening of a knee even between attacks developed.

"METABOLIC ARTHRITIS"

No articles appeared under this vague title.

ENDOCRINE ARTHRITIS

Acromegalic Arthritis. The gross and microscopic findings in joints of an acromegalic patient were reported by Waite, Bennett and Bauer. Although the degree of hypertrophic reaction of bone in most peripheral joints was striking, the process conformed essentially to the familiar pattern of marked degenerative joint disease (osteoarthritis). But in certain sites the changes appeared to be distinctive and could not be regarded as reactions to primary degeneration of cartilage. New growths of cartilage and bone appeared to indicate reactivation of cartilage growth and enhanced endochondral ossification, unphysiologic at the age of the patient, and perhaps the result of a specific hormonal stimulus.

[These findings were compatible with those of Erdheim who, in 1931, first directed attention to the relationship between pituitary tumors and a specific form of articular disease. The acromegalic spine is characterized by additional growth of vertebral bodies. Newly formed bone, more evident on anterior and lateral aspects of vertebrae, is demarcated clearly in roentgenograms.—Ed.]

"Menopausal Arthralgia or Arthritis." The confused nomenclature regarding articular symptoms experienced during the menopause was well illustrated by one author's reference to "menopause arthralgia"⁹⁰⁰ and "menopause arthritis"⁶⁹⁹ in two separate reports appearing simultaneously. [These reports presumably concerned the same, or a similar, group of patients. No clinical or pathologic definition of either menopausal arthritis or arthralgia was given. Symptoms were not described or differentiated from those of periarticular or intramuscular fibrositis or of osteoarthritis. To our knowledge no distinctive pathology of "menopause arthritis" has ever been demonstrated.—Ed.] "The menopause does not cause rheumatism and there is no such entity as 'menopausal arthritis.' At the change of life any of the main types of rheumatic diseases may first manifest themselves," so wrote Bach.⁴⁷ He and Freyberg stated that women with skeletal symptoms at the menopause rarely exhibit definite articular changes except mild osteoarthritis⁴⁷ [occasionally spinal osteoporosis—Ed.]. Although denying the exist-

ence of "menopause arthritis" Freyberg⁶⁰⁵ considered "menopause arthralgia" separate from "fibrositis" [neither clinically defined—Ed.] and noted "improvement" in five (83 per cent) of six cases of "arthralgia," in only four (57 per cent) of seven cases of "fibrositis" treated with estrogenic substance. Others^{47, 900} considered estrogens of value for the arthralgias of menopause.

Other Endocrines or Hormones. An interrelationship between "hypocortico-adrenalism" or hyperthyroidism and diseases of joints or muscles was suggested by Lyon¹¹³⁸ who noted improvement in three patients with musculoskeletal symptoms (one unclassified, two with ankylosing spondylitis) treated with adrenal cortical extracts. [The evidence presented was not convincing.—Ed.] According to Freyberg⁶⁰⁵ disturbances of thyroid, parathyroid or adrenals produce no specific type of arthritis and bear no direct or significant therapeutic relationship to any recognized type of acute or chronic arthritis.

PALINDROMIC RHEUMATISM

A "new," rather rare, oft-recurring disease of joints was described by Hench and Rosenberg⁸¹⁸ under the title "palindromic rheumatism." The word "palindromic" which means "recurring" or "returning," was first used in the Hippocratic corpus in a nonspecific sense, and is defined in current Greek lexicons to mean "recurring" or "subsiding without coming to a head." Thus the term described the most obvious and characteristic feature of the condition, its frequent recurrences, attacks and retreats.

Chief features were multiple, afebrile attacks of acute or subacute arthritis and peri-arthritis, sometimes also para-arthritis, with pain, swelling, redness and disability usually of only one, sometimes of more than one, small or large joints of adults of either sex. Attacks appeared suddenly, developed rapidly and generally lasted only one or two days (occasionally a little longer), then disappeared completely but recurred at short or long irregularly spaced intervals. Despite the transitory presence of an acute or subacute inflammatory cellular exudate in articular tissues and cavity, little or no constitutional reaction or abnormality in laboratory tests and no significant functional, pathologic or roentgenographic residues were present even after years of disease and scores or even hundreds of attacks.

Clinical and Laboratory Data. Thirty-four cases were described in patients (19 females, 15 males) aged 13 to 68 years but usually between 20 and 40 years of age.

The disease had lasted an average of seven years: 16 to 25 years in four cases, six to 15 in 15, one to five in 10, less than one year in five but in each of these five from 10 to 130 attacks had occurred. The frequency of attacks varied from 10 in nine months to "thousands" in seven years. *Yearly* attacks numbered two to 10 in nine cases, 20 to 60 in 17, 100 to 200 in three, and 250 or more each year in five cases. Joints affected were usually only one in 85 per cent of cases, sometimes more. Favorite sites were fingers including terminal phalangeal joints, a wrist, shoulder, knee, toe or elbow; almost any joint was occasionally involved. The onset of attacks was at any hour but frequently "vesperal." Pain varied from mild to severe, sometimes requiring narcotics. Local disability was usually considerable; when a lower extremity was affected, 14 patients were temporarily bedridden. The usual duration was a few hours to three days; occasionally three to seven days.

Para-arthritis, red, tender swellings near an affected or nonaffected joint, occurred in 30 per cent of cases; finger pads were occasionally swollen and hot. In three severe cases intracutaneous or subcutaneous nodules (3 to 8 mm. in diameter) appeared, usually on hands, occasionally elsewhere; sometimes they lasted only a few days; sometimes they persisted. There was no anemia, leukocytosis or eosinophilia; there was often a relative lymphocytosis (37 to 48 per cent). Sedimentation rates were usually normal between attacks, generally but not always slightly elevated (usually 18 to 35 mm. at one hour; Westergren technic) during attacks. There was a moderate elevation of fatty acids (368 to 569 mg. per 100 c.c.) and total lipoids (448 to 884 mg. per 100 c.c.). Blood uric acid, calcium, phosphorus and phosphatase were normal. Roentgenograms of affected joints were consistently negative even in those patients who had hundreds of attacks within 15 to 25 years.

The condition was distinguished from "angioneural arthrosis" (Solis Cohen, 1913), the "allergic rheumatism" of Kahlmeter (1939), gout and rheumatoid arthritis. Three of the patients were physicians who had long abandoned the idea that they had rheumatoid arthritis.

Pathology. Studies, limited in number, revealed: during attacks acute or subacute cellular reactions in synovial membrane, capsule or tendon sheath, sometimes fibrinopurulent synovial exudate; between attacks normal tissues; no pannus or destruction of cartilage, no follicle-like collections of lymphocytes or urates, and no eosinophilia in tissues.

Treatment. Many remedies were tried without notable results: adrenalin, ephedrine, benzedrine, ergotamine tartrate, histamine, histaminase, typhoid vaccine, removal of foci, sulfanilamide. One patient considered calcium gluconate (100 grains or 6.5 gm.) daily useful; another "adopted a baby, quit worrying and was cured."

Prognosis. End results in 27 cases (total duration of disease, 307 years) were: spontaneous cure in 15 per cent, attacks shorter or less frequent in 44, disease unchanged in 26, attacks more frequent in 11 per cent, and death from coronary disease in one case (4 per cent). There appeared to be no tendency for the disease to become continuous in any joint. The disease was a handicap to some, a nuisance to many, a cause of residual deformity or crippling in none.

Subsequent Data. Since the first report by Hench and Rosenberg 19 cases of supposed palindromic rheumatism have been reported in nine papers (Thompson¹⁷⁹³; Mazer; Vaughan¹⁸⁵⁰; Ferry; Paul and Logan; Grego and Harkins; Cain; Wingfield; Paul and Carr). Nine cases were reported in detail; 10 were merely mentioned in one report (Vaughan¹⁸⁵⁰). Of those described in detail eight cases conformed to the criteria of Hench and Rosenberg, except that in one case sedimentation rates were higher than usual in one attack (Wingfield).

Of the nine detailed cases seven were in males, two in females, a sex ratio unlike that in rheumatoid arthritis. In the eight characteristic cases the disease had lasted from one to 32 years (one, four, five, seven, seven, 13, 30 and 32 years) without producing clinical or roentgenographic evidence of residual arthritis, during which time the patients had had from 100 to more than 1,000 attacks. Attacks lasted usually one to three days, occasionally one hour to 10 days. Usually only one joint was affected but attacks in any case were scattered. Sedimentation rates were almost always normal even during attacks. The latter were usually afebrile; temperatures of 99 and 99.2° F. were rarely noted. Para-arthritis affected two, nodules none. No biopsies were made.

One case (Paul and Logan¹³⁵²) may have been a case of early atypical episodic rheumatoid arthritis rather than of palindromic rheumatism: there was anemia (hemoglobin, 11 gm.; erythrocytes, 3,780,000); the patient had lost 30 pounds (13.6 kg.); attacks lasted "several hours to several days" and at times several joints were afflicted simultaneously. Even so attacks continued to disappear completely according to a later report (Paul and Carr¹³⁵¹). Discussing 27 cases of supposed (recurrent) allergic arthritis Vaughan¹⁸⁵⁰ stated that in 10 the condition "fairly closely" resembled palindromic rheumatism and he concluded that food or inhalant allergens might be a chief cause of palindromic rheumatism.

[The individual cases were not described; data sufficient for an independent appraisal were lacking.—Ed.]

Nothing new on etiology was offered in these reports. An allergic factor seemed important to some^{1352, 1850} but not to others.^{552, 702, 1181, 1351} Emotional stress from hard work and other psychic factors were noted in several cases.^{552, 1181, 1351, 1852}

Treatment was symptomatic in most cases; none was given in some. Oxyiodide (cinchophen hydroiodide) seemed useful in one case.¹³⁵² Cinchophen was avoided by others.⁵⁵² Heat made one patient worse.⁵⁵² No results were obtained from epinephrine,²⁷⁸ sulfathiazole, contramine (a sulfur compound) or salicylates.¹⁰⁴⁴ Special diets were recommended by Vaughan.¹⁸⁵⁰

These reports have been partly responsible for the greater attention recently paid to certain cases of atypical rheumatoid arthritis the likes of which are generally not described in articles or texts. In addition to the usual form of rheumatoid arthritis (insidious onset, chronic progression with variable severity but incomplete remissions) and the less common acute or subacute febrile rheumatoid arthritis (sudden onset, acute or subacute arthritis lasting a few weeks or months; generally complete remission; the "infective arthritis" of British texts), another form is now being recognized and might be called "episodic (atypical) rheumatoid arthritis." It is characterized by many short attacks, separate or concurrent, with little or no evidence of residues at first, later usually chronicity and residues.

[Ropes and Bauer¹⁴⁰⁵ believe that most, if not all cases of palindromic rheumatism are really cases of atypical rheumatoid arthritis. One might argue that rheumatoid arthritis is a variable disease with differing patterns of severity and chronicity in this order: (1) palindromic rheumatism or "palindromic type of rheumatoid arthritis," persistently remitting completely; (2) episodic rheumatoid arthritis (episodic and completely remitting in some joints, chronic in a few, at least in time); (3) subacute febrile rheumatoid arthritis with notable remissions, and (4) ordinary chronic progressive rheumatoid arthritis. Those inclined to this view would regard palindromic rheumatism, not as a separate entity but as a (newly described) variety of atypical rheumatoid arthritis, perhaps a "forme fruste." They might prefer to speak of "the palindromic phase (or type) of rheumatoid arthritis."

The exact position of palindromic rheumatism and its relation (if any) to rheumatoid arthritis cannot be established until the cause of either or both is known. Meantime it seems worth while to study this type of articular disease and to differentiate it descriptively, not only from (ordinary) rheumatoid arthritis but also from "episodic rheumatoid arthritis." One of us, P. S. H., believes that in most cases a valid differentiation can be made rather readily. Thus: in palindromic rheumatism the attacks are anatomically scattered; para-arthritis frequently occurs, finger pads are

sometimes affected; attacks usually last only one or two days; intervals between attacks are weeks or months as a rule, and during the intervals articular and constitutional signs and symptoms are absent. Articular biopsies reveal changes not supposedly characteristic of rheumatoid arthritis. In "episodic rheumatoid arthritis" the "attacks" tend to recur in favored sites; para-arthritis is not notable; involvement of finger pads has not been seen. Some attacks tend to last longer (frequently several days, occasionally weeks) and the intervals between attacks are shorter (and often tend to become increasingly shorter) than in palindromic rheumatism. In episodic rheumatoid arthritis symptoms between attacks (mild tenderness, stiffness, slight residual thickening) are often present but are ignored or discounted by a placid patient or by a physician fearful of the correct diagnosis. Between attacks elevated sedimentation rates and constitutional symptoms are often present (anemia, loss of weight, undue fatigue) even if joints are free or relatively so. Roentgenograms of a now painless, but formerly affected, joint may be "positive," not persistently normal as in palindromic rheumatism. Finally, articular biopsies in the episodic cases may reveal changes suggestive or characteristic of rheumatoid arthritis.—Ed.]

EPIDEMIC TROPICAL ACUTE POLYARTHRITIS

("FOX-HOLE ARTHRITIS"; "BOUGAINVILLE RHEUMATISM")

Historical Data. In September, 1942, a "new form" of rheumatism appeared among Australian soldiers in the Darwin-Adelaide River area of the Northern Territory of Australia. Its four chief features were acute polyarthritis, mild fever, transient rash and lymphadenopathy. At first it was thought to be rheumatic fever. Cases increased in October, and in December, 1942, it affected 24 American and five Australian soldiers in the Birdum Larrimah region of Northern Australia. These 29 patients were studied at the 135 Medical Regiment Hospital by Hidde⁸⁴¹ who regarded the condition as a new entity and reported it on January 29, 1943, to the Surgeon General of the United States Army. The report was a "secret paper" and not published.

The disease spread through the Northern Territory of Australia and slowly spread south to affect military units along the Darwin Tenants Creek Road. Near the end of January, 1943, the first case was reported from the Mt. Isa region, 800 miles south of the place of origin. Meanwhile cases were increasing among Australian soldiers in the Northern Territory and between November 1, 1942, and January 31, 1943, 105 patients with it were admitted to two Australian army hospitals and studied by Halliday and Horan, of the Australian Medical Corps, whose report, apparently made independently and without knowledge of Hidde's report, was published on October 9, 1943.

Another small epidemic occurred during November and December, 1943, in the Northern Territory mostly within a radius of 30 miles of the Adelaide River area. A brief summary of about 65 cases was reported by Harris.⁷⁷⁵ In February and March, 1944, the disease spread east and appeared in Queensland; 28 cases were reported by Sibree. In March and April the disease first appeared outside Australia and affected American troops on Bougainville; no cases were reported from other South Pacific islands.⁵³³

In the Bougainville epidemic (March to May, 1944) about 124 American and a few Fiji soldiers were affected; Negro troops were unaffected. At the Twenty-First Evacuation Hospital 41 cases were analyzed by Mulvey¹²⁷⁰ and McCarry.⁵³⁵ That fall (October) the disease reappeared, this time in the Oro Bay area near Buna in New Guinea where 20 or more American soldiers were affected.⁵³⁶

The soldiers had nicknamed their disease "fox-hole arthritis" or "Bougainville

rheumatism." Terms used in medical reports were "acute polyarthritis," ^{742, 841, 1605} "polyarthritis," ⁷⁷⁵ "acute arthritis," ¹²⁷⁰ "acute polyarthritis with eruption." ⁵³⁶

[The term "epidemic tropical arthritis" was recently suggested by one of us, D. C. C.; perhaps the term "epidemic tropical acute polyarthritis" would be even more suitable.—P. S. H.]

Clinical Data. A total of more than 371 cases were noted in these seven reports. Except for minor variations, the clinical features of all cases were similar.

Of gradual onset, initial symptoms were pains, sometimes redness and swelling, of many peripheral joints. Involvement of midphalangeal joints of fingers sometimes resembled acute rheumatoid arthritis. Usually following, but sometimes preceding the acute polyarthritis was a maculopapular rash somewhat resembling rubella or chickenpox. Rupture of vesicles or desquamation did not occur. Tender enlargement of lymph nodes and a mild fever (99° to 101° F.) were present. In most cases the conditions cleared completely within 10 to 20 days. No residual cardiac or articular damage resulted.

Etiology. This was not determined. Facilities for intensive studies on etiology were lacking in American field hospitals. But agglutination tests with *Proteus* OX19, XK and OX2 strains and for *Brucella abortus* were negative (Halliday and Horan; Hidde). Halliday and Horan reported cultures of blood, joint fluid, urine, stools and tonsils to have been negative. The seasonal periodicity of the epidemics was of interest. It appeared each year for three successive years with the onset of the hot season and stopped abruptly with the onset of heavy rains. [The rainy season starts in November and is marked in January and February.—Ed.] This suggested the factor of an insect vector but no proof was found. The disease is probably endemic in the Northern Territory but its occurrence has gone unnoticed because the peacetime population was small.

Differentiation. Considered were rheumatic fever, Haverhill fever and dengue. No streptococcic pharyngitis preceded the disease; response to salicylates was poor. The rash was more extensive than that seen in dengue; pains were articular, not osseous and the postdengue exhaustion was absent.

Treatment. Symptomatic treatment was employed.

REITER'S SYNDROME (URETHRITIS, CONJUNCTIVITIS, ARTHRITIS)

The first report in the English literature on this clinical syndrome [except for a reprint from a German article by Fruehwald—Ed.] was based on six cases observed by Bauer and Engleman and a review of 20 authentic cases reported in foreign literature. The clinical course of this syndrome of unknown etiology is characterized by urethritis, purulent conjunctivitis and arthritis (and at times, diarrhea). Ten cases were observed subsequently among personnel at a naval station (Rosenblum) and 25 cases were reported from an army rheumatism center* (Hollander, Fogarty Abrams and Kydd). [In many of the latter cases the triad of symptoms were not present and, therefore, they should not have been included as cases of Reiter's syndrome.—Ed.] Other cases were noted among military personnel and civilians. ^{115, 257, 637, 1081, 1129, 1240, 1735}

• Affected have been young men, aged 20 to 30 years. Usually purulent urethritis, but sometimes conjunctivitis, marks the onset of the disease. Urinary and ocular

symptoms are generally short-lived. The arthritis is persistent and disabling, involving several weight-bearing joints most frequently, though monoarthritis does occur. Constitutional symptoms are usually mild. The disease runs a self-limited course; attacks last one to five months. Recurrences months or years later occur in 25 per cent of cases and may involve any or all of the three systems.⁹¹ Renal complications may occur¹²⁴⁰; pyelonephritis affected a kidney removed for hydronephrosis.³⁵⁷ Skin lesions resembling erythema multiforme¹⁵⁰⁴ and keratosis blenorragica¹⁰⁸¹ have been reported as features of Reiter's syndrome, and Reiter's disease was considered identical with "nongonorrheal keratosis blenorragica" by some.¹¹²⁹ [Important deviations from the accepted clinical picture make one question the diagnosis.—Ed.] The association of diarrhea with the usual triad of arthritis, conjunctivitis and urethritis was commented on^{91, 858} and led one author to the unproved conclusion that "Reiter's disease appears to be nothing more than the familiar dysenteric polyarthritis with superadded toxic manifestations."¹¹⁵

Synovial fluid examinations showed alterations observed in the specific arthritides.⁹¹ Bacteriologic examinations of urethral, prostatic and conjunctival exudates, and synovial fluids were negative for gonococci; urine and blood cultures have been sterile.⁹¹ Biopsy of a joint during the acute phase revealed markedly injected synovial membrane with intense hyperemia and small focal areas of acute inflammatory cellular infiltration (Bauer and Engleman). The roentgenograms showed bone atrophy of varying degree and, rarely, circumscribed areas of subchondral atrophy.

The etiology is unknown. The possibility of a staphylococcic etiology was suggested without adequate evidence.⁶³⁷ The allergic and toxic theories^{115, 637} also were unsubstantiated. Bauer and Engleman⁹¹ favored an infectious origin, although they did not demonstrate the agent. [Subsequent studies being done by one of us, W. B., and his colleagues (Dienes and Smith^{468, 469}) suggest that pleuropneumonia-like organisms may be related to Reiter's syndrome.—Ed.]

Treatment with sulfonamides and penicillin was without benefit.^{91, 858, 1240, 1504} Induction of febrile reactions by intragluteal injection of boiled milk¹⁷³⁵ and "arthrignon"¹¹⁵ presumably resulted in marked clinical improvement. [Evidence to substantiate the value of such treatment is lacking.—Ed.]

[This is another example of the confusion that may arise if an eponymic designation becomes attached prematurely to an original incomplete clinical description. In 1916 Reiter reported one case of diarrhea, acute urethritis, conjunctivitis and arthritis in a young army officer; reportedly cultured from the blood was a spirochete (forans) not found in controls. Mice infected with the spirochete developed an acute illness with marked sweating but apparently no articular, ocular or intestinal lesions." The patient also had sweat considerably. On this evidence Reiter concluded that the spirochete caused the patient's disease which he named "spirochetosis arthritica." Twenty-five years later (1941) Reiter saw fit to report again the same original case with no additions whatever. Meanwhile European writers had described under various titles, especially "Reiter's disease," cases in which variable clinical features were present. Most of these have been rejected by Bauer and Engleman⁹¹ as not representing the syndrome. In general the diarrhea of Reiter's quadriad was not included and reports spoke of the "classical triad." A spirochetal origin was not confirmed.

Current American reports have likewise been confusing: there has been no agreement as to the clinical content, as to whether the arthritis is acute or subacute with complete remissions or progressively chronic with destructive residues, roentgenographically similar to rheumatoid arthritis. Some writers insisted that any one or even two features of the "classical triad" may be absent; others have reported as

Reiter's disease cases of chronic arthritis with skin lesions and without urethritis, conjunctivitis or diarrhea. During the war Short noted among troops in North Africa 20 cases of dysentery and acute polyarthritis and 10 cases of polyarthritis, dysentery and urethritis or conjunctivitis or both. The condition was suggestive of Reiter's syndrome, but since stool cultures and agglutination tests incriminated the *Shigella* dysentery bacillus, the question arose as to whether Reiter's syndrome might represent latent Shiga dysentery. Others (Beiglböck) have commented on the ocular and urinary complications of "dysenteric arthritis" (Flexner) and Manson-Bahr,¹¹⁵ commenting on Beiglböck's paper, concluded that "Reiter's disease appears to be nothing else than the familiar dysenteric polyarthritis with some superadded toxic manifestations which have been previously described." But dysenteric arthritis is not common and cases in which dysentery bacilli have been recovered from joints are rare. Perhaps Short's cases were not of dysenteric arthritis.

Cases of undoubted rheumatoid arthritis are complicated not infrequently by ocular lesions, occasionally by nonspecific urethritis or a brief diarrhea (see past Reviews¹). Until we have more data and greater agreement as to the clinical definition, and in the absence of a diagnostic test or known cause, one should hesitate to make a diagnosis of "Reiter's syndrome." But such studies should be continued especially since certain strains of pleuropneumonia-like organisms are susceptible to streptomycin.—Ed.]

PHARMACEUTIC ARTHRITIS AND ARTHRALGIA

Articular Reactions to Sulfonamides: "Sulfadiazine Arthritis." Most reactions to sulfonamides do not involve joints but three cases of febrile sulfonamide arthralgia were noted.

Fever, chills and polyarthritis developed in a case of chronic ulcerative colitis during each of four courses of sulfathiazole but not during later use of sulfaguanidine or succinyl sulfathiazole. The articular complication was from the drug, not from the colitis.¹⁰²² Two cases of sulfadiazine arthritis occurred among 134 of meningococcal infections treated by Marangoni and D'Agati.¹¹⁵³ One patient with meningitis had muscular and articular soreness without swelling. Various symptoms were relieved by sulfadiazine but after six days of therapy elbows and wrists suddenly became swollen, tender, painful and hot. Because of persisting arthritis and fever, doses of sulfadiazine were stopped on the thirteenth day. In 36 hours articular symptoms disappeared. "Arthritic pain" affected only three (0.6 per cent) of 500 patients given sulfadiazine; the pains promptly subsided on cessation of the drug.¹⁵³⁵

Articular Reactions to Penicillin. Recently reported were one case of prompt, and several of delayed, sensitivity to penicillin with articular reactions like those of serum sickness. Present were moderate fever, painful polyarthritis, urticaria or pitting edema, sometimes erythema, adenopathy and dyspnea. Such reactions usually began seven to 14 days after penicillin therapy was instituted, sometimes five to nine days after its brief use was stopped, but in one case⁹¹¹ twice within 48 hours after therapy was begun. Reactions lasted four or five days and were usually relieved by epinephrine alone or epinephrine in oil with the supplemental use of pentobarbital sodium or phenobarbital.^{387, 409, 681, 735, 911, 1140, 1414}

Serum Sickness. Serum sickness involving temporomandibular joints resulting from tetanus antitoxin must be differentiated from onset of inadequately controlled tetanus. On a correct differentiation may depend the patient's life.

Turner and Clarke reported three cases of acute temporomandibular arthropathy (two after tetanus antitoxin, one after antipneumococcus serum). In one case a choice had to be made between risking death from tetanus (if the arthropathy represented impending "lockjaw" and if further antitoxin were withheld) or death from anaphylactic shock (if the arthropathy represented serum sickness and more antitoxin were given). The mechanism of serum sickness was studied by Karelitz, Glorig and Stempien.^{951, 952} Patients convalescing from serum sickness after treatment with horse serum possess antibodies capable of passively sensitizing normal persons to horse serum.

OSTEOCHONDRITIS

Osteochondritis of Growth Centers. Varieties of this condition have, until recently, been regarded as separate disease entities and have acquired various eponymic designations (Osgood-Schlatter disease; Legg-Calvé-Perthes' disease). To emphasize their fundamental similarity some writers grouped them as "osteochondritis of growth centers."¹⁰⁹¹ Almost every growth center in the body can be so involved. The osteochondritis probably results from any one of several causes.⁶⁵¹ Insufficiency of the blood supply to the involved epiphysis may play a causal rôle more important than trauma. Hypothyroidism was not a factor.⁶⁵¹

Osteochondritis of the terminal phalangeal epiphysis of a finger of a child was noted (Staples¹⁰⁹¹). Reports on osteochondritis juvenilis of acetabulum are scarce: five cases (without involvement of adjacent femoral heads) were reported; in one the lumbar spine was also affected.¹¹¹³ Legg-Perthes' disease was discussed briefly.⁶⁸⁹

Traumatic Osteochondritis (Chondromalacia) of Patella. When a direct blow affects the patella its subchondral bone is compressed and areas of necrosis may develop therein and in femoral condyles. Repair may occur or the injured bone may be walled off and form a sequestrum. The following may then occur: gross interference with nutrition of overlying cartilage, degeneration of cartilage, irritation and hypertrophy of synovium with effusion, late progressive osteoarthritis (Cox).

Six cases were described.³⁰⁹ Weeks or months after the acute posttraumatic symptoms subsided, mild chronic effusion appeared with vague pain in knees especially in the anterior compartment of the patella on kneeling or squatting. All patients noted occasional "locking" or "catching." Synovium was palpably thickened; synovial effusions and muscular atrophy varied in amounts. Crepitation or grating was elicited on passive motion of patella over femoral condyles. Pressure over patella or passive motion of patella caused pain. Roentgenograms were essentially negative although pathologic changes included: softening, fissuring and discoloration of cartilage of patellae and the anteromedial aspects of femoral condyles; thickening and villous degeneration of the synovium of suprapatellar pouch and anterior compartment of knee joint; pannus at edges of cartilage of patellae and femoral condyles; hypertrophy of infrapatellar fat pads.

The cartilage degeneration is not the primary lesion but is secondary to that in subchondral bone.³⁰⁹ To relieve symptoms and prevent secondary osteoarthritis later in life patellectomy was preferred by Cox to patellaplasty (simple resection of affected cartilage): the six patients were completely relieved even though affected synovium, fat pads and femoral condyles were untreated.

[Patellar chondromalacia is the probable cause of many "squeaky knees."—Ed.]

To show the articular surface of patella and femoral trochlea a special roentgenographic technic (with the knee bent) was recommended.¹⁰⁵³

Traumatic Osteochondritis of Professional Baseball Pitchers. Osteochondritis with loose bodies in the olecranon fossa often develops in elbows of baseball pitchers. Semidetached bodies also appear near the internal condyle and irritate the ulnar nerve. Surgical removal of loose bodies relieves symptoms and restores function (Bennett¹²³).

Osteochondritis Dissecans. This refers to "an osteocartilaginous lesion of debatable etiology, characterized by a partial or complete demarcation of a segment of articular cartilage and subchondral bone, with or without ultimate detachment and extrusion into the joint." The literature was reviewed¹⁶⁹⁸ and 24 cases described: 20 in knees^{286, 1063, 1698, 1736}; four in astragalus.^{320, 347}

The condition results from posttraumatic necrosis of subchondral bone rather than from embolism or from osteochondral fractures, according to current writers.^{347, 1698} Roentgenograms may be negative for as long as six months after the causal injury; in the absence of roentgenographic changes Langton¹⁰⁶³ considered diagnostic a typical history, tenderness over the point on the condyle likely to be affected, crepitus, a wasted quadriceps. Conservative treatment (rest, immobilization) was recommended for "slumbering," relatively symptomless cases¹⁶⁹⁸ and was successful in a child, aged four and one-half years.¹⁷³⁶ To prevent synovitis and later osteoarthritis, arthrotomy and removal of loose bodies was recommended⁶³⁹; excision of affected bone and cartilage was reserved for selected cases.¹⁶⁹⁸

Tuberculous Osteochondritis of Ribs. Roentgenographic diagnosis of osteochondritis in the anterior ends of ribs can be made by making tangential exposures. Results in 12 cases of proved and 26 cases of probable osteochondritis of ribs were reported (Lindblom¹¹⁰¹).

"SYNOVITIS" AND SYNOVIAL CYSTS

No data appeared under "synovitis."

Synovial Cysts of Fingers. Called "synovial cysts," "synovial lesions of skin," "recurrent myxomatous cutaneous cysts," "periarticular fibromas of skin," these are fairly rare, but are occasionally associated with Heberden's nodes. Roentgenographic studies with diodrast showed a cyst connected with the joint. Eliassow and Frank concluded that "synovial lesions of the skin are due to an escape of synovial fluid from the joint cavity."

[Chemical and cytologic analyses were not made to determine whether the cystic fluid had the characteristics of synovial fluid. The small amounts of cystic fluid usually available would make such analysis difficult. One of us, W. B., found the fluid in such a synovial cyst to have a much greater content of calcium and to be much more viscous than normal synovial fluid.—Ed.]

Synovial Cysts of Popliteal Space; "Baker's Cysts." 1. *Definition.* Confusion as to the exact nature of Baker's cysts, popliteal or synovial cysts of the popliteal space was exhibited. In 1877 and 1885 Baker⁶² described synovial cysts in the leg with disease of the knee; he stated that the cysts resulted from osteoarthritis. Later others reported a variety of popliteal enlargements as "Baker's cysts."^{1039, 1235} Recent opinions were that Baker's cysts consist of (1) a posterior herniation of the capsule of knee (Kuhn and Hamphill¹⁰³⁹);

(2) hernial protrusion of synovial membrane from the superior tibiofibular joint (Whalley); (3) semimembranous bursitis (Cottrell); (4) "enlarged semimembranosus bursa" (Burman²⁵⁸); (5) *either* posterior herniation of articular capsule (63 per cent of cases) *or* semimembranosus bursa enlarged by "hyperplasia-fluid distention" (37 per cent; Haggart^{731, 732}); (6) generally "herniation of synovial membrane through posterior part of the capsule, or, less commonly, enlargement of either the semimembranosus or the medial gastrocnemius bursa by an escape of synovial fluid from the knee into either of these bursae via the normal anatomic connections between knee and bursae" (Meyerding and Van Demark). Because the term has been so misused or applied to so many different conditions, it was suggested that "the confusing patronym of Baker's cyst should be dropped" in favor of the more inclusive "popliteal cysts" (Burman²⁵⁸).

The popliteal cysts of children usually consist of enlarged semimembranosus bursae, those of adults usually comprise posterior herniations.^{731, 732} Swelling from an enlarged semimembranosus bursa is more obvious on the medial side of the popliteal space; that from herniation is at or near the midline^{731, 732}; other popliteal conditions to be differentiated were discussed.¹²³⁵ Neuritis with foot drop was caused in one case by compression of the external popliteal nerve by a Baker's cyst.¹⁹¹⁷

2. *Pathology.* According to Meyerding and Van Demark cysts were lined by endothelium but according to Haggart,^{731, 732} sac linings, whether of herniations or bursal enlargements, were "mesothelial similar to the synovial membrane of the knee." That described by Whalley had a hyaline fibrous wall with no endothelial or epithelial lining. Even those who spoke of the bursal enlargements as "simple fluid-distentions" or "hyperplastic bursae" admitted that an acute or chronic inflammatory reaction of the serous and subserous layers of either bursae or synovial herniae often was present.^{731, 732, 1235} Presumably the herniae or bursae contain synovial or synovial-like fluid but Ghormley and Dockerty⁶⁴⁴ noted four "Baker's or popliteal cysts" which contained, not synovial fluid, but a solid mucinous (gelatinous or myxomatous) content; hence they were classified as "endothelial cysts."

3. *Etiology.* Trauma was considered the chief irritant by some^{258, 731, 732} but not by Meyerding and Van Demark¹²³⁵ in seven of whose 15 cases rheumatoid or osteoarthritis of the affected knees was present. But if arthritis were a significant cause of "popliteal cysts," Burman²⁵⁸ thought their coexistence would be more common.

4. *Differentiation and Treatment.* For accurate roentgenographic differentiation pneumograms were recommended by some,¹⁰³⁹ considered irritating or useless by others.^{731, 732, 1235} Preferred treatment was surgical excision and closure of articular communications.^{644, 731, 732, 1039, 1235} Small cysts producing mild symptoms may be treated by pressure pads.¹⁰³⁹ Use of sclerosing solutions was not approved.¹⁰³⁹

TUMORS OF SYNOVIA AND OTHER ARTICULAR TISSUES

Hemangioma. Only 29 cases had been reported through 1939.¹⁸ In eight new cases^{328, 764, 1863, 1990} two types were recognized: a diffuse form limited to synovial membrane, and a cavernous form with invasion of adjacent fascia and muscles. Features are characteristic: intermittent pain and swelling of a single joint usually since childhood; pain is usually mild; swelling and pain are augmented by standing, relieved by elevation of leg or compression of joint. Differentiation from hemophilic arthritis is important. Preferred treatment was

excision for the local (pedunculated) type, roentgen therapy for the cavernous type.

A "hemangioma of the elbow" in an infant 10 weeks old was successfully treated with radium.⁹¹⁵ The large ulcerating hemangioma was noted at birth over the left elbow "and forming part of the soft tissues of the elbow joint." [No roentgenographic or pathologic evidence was presented to show that the tumor was intra-articular.—Ed.]

Xanthoma. Xanthomas (giant cell tumors) affect tendon sheaths more often than synovial membranes or bursae; 25 new cases were reported.^{407, 838, 1083} Jaffe, Lichtenstein and Sutro^{906, 907} used the terms "pigmented villonodular synovitis, bursitis and tenosynovitis" to link tenosynovial xanthomas to the synovial and bursal lesions variously called "chronic hemorrhagic villous synovitis," "giant cell fibrohemangioma," "benign or malignant polymorphocellular tumor of synovial membrane."

Cystic Myxomatous Tumors. Reported were four cases of unusual mucinous tumors of knees including two which were probably cysts of menisci, examples of degeneration rather than true neoplasia (Ghormley and Dockerty). Endothelial linings were absent.

Synovioma (Synovial Sarcoma). 1. *Clinical Data.* Aitken⁹ reserved the term "synovioma" for tumors derived primarily from cells of synovial lining and characterized by the formation within the tumors of spaces lined with synovial cells. It is a sarcoma, highly malignant or potentially so. Reviews of 76¹⁰⁷¹ and 104⁷²² collected cases appeared. More than 50 new cases were described.^{9, 109, 211, 462, 539, 502, 708, 722, 730, 788, 834, 889, 906, 1071, 1075, 1262, 1658, 1690} Included was the largest single series (16 cases) so far reported.⁴⁶² The term "synovium" has been stretched to include linings of tendons and bursae as well as of capsules; hence, some of the "synovial sarcomas" reported were of tendons or bursae.⁹⁰⁶

Of all previously reported cases knees were affected in 47 per cent^{722, 1071}; lower extremities in 79 per cent of 104 cases; upper in 21 per cent. Symptoms were considered characteristic by some:⁵³⁹ steady boring pain not relieved by rest or heat, progressive articular enlargement, flexion deformity of knee. But the chief features (pain, tumor, joint dysfunction, occasional effusions) were considered not characteristic by others.⁴⁶² Diagnoses are seldom made before surgical examination. Lewis¹¹ described roentgenographic features pathognomonic of synovioma: scattered, irregular deposits of amorphous lime within a soft-tissue tumor-mass; these features were present in Aitken's case.⁹ Most lesions are malignant.⁷⁸⁸ Two benign lesions involving bursae were noted.^{708, 834} Data on 45 collected cases of sarcoendothelioma were reviewed (Fisher⁵⁶²). A pathologic classification⁴⁶² and a method for culturing synovial sarcomas in vitro were described.¹²⁸³

2. *Treatment.* In selected cases excision was considered feasible,²¹¹ but recurrences and metastasis usually follow.⁴⁶² Since most synoviomias are resistant to radiation this was generally not recommended. No five-year cures have resulted from radiation alone, which does not even provide palliative relief.^{708, 722} Amputation was considered necessary only in selected cases.^{9, 211} generally necessary.^{1658, 1690} or the treatment of choice for all synovial sarcomas, although "delayed amputation" to allow for thorough histologic study of excised tissues is sometimes justified.⁴⁶² After reviewing results in 104 collected cases

Haagenson and Stout⁷²² recommended high amputation and possible dissection of regional nodes.

3. *Prognosis and End Results.* These were statistically discussed.^{722, 1071} Five-year cures are uncommon. Metastasis generally affects lungs. One patient treated by excision alone (Haggart⁷³⁰) and one by "delayed amputation"⁷²² were well eight years after treatment.

4. *Chondromatous Metaplasia of Synovia.* One case was reported. Roentgenograms of knee showed "follicular calcification" in soft tissue. Diagnosis was impossible without biopsy. Multiple round foci of hyaline cartilage were developing in synovia.¹¹⁶⁹

5. *Pseudotumors in Synovia.* Two cases in knees were noted, one of "synovitis villosa hemorrhagica chronica" and one of benign synovial histiocytoma.¹²⁴⁶

6. *Synovial Osteochondromatosis.* Removal of loose bodies is necessary to prevent secondary osteoarthritis.⁶³⁹

7. *Malignant Lymphosis of Joints.* No new data on leukemic infiltrations of articular tissues were reported.

8. *Nonleukemic Myelosis.* A patient entered the hospital seven times "because of 'rheumatism'": fever, pains in arms, legs and back. No articular swellings developed. A rare condition was present: chronic nonleukemic myelosis (Carpenter and Flory²⁹²).

MISCELLANEOUS TYPES OF JOINT DISEASE

Clubbing and Hypertrophic Osteoarthropathy. Clubbing and hypertrophic osteoarthropathy, once considered independent phenomena, are related; the osseous changes of the latter represent a more advanced stage of the former process. An excellent review of their pathogenetic relationships was made by Mendlowitz. Various forms of clubbing and osteoarthropathy were described. Osteoarthropathy is much less common than simple clubbing.

Clubbing may be symmetrical, unilateral or unidigital. Symmetrical clubbing may be hereditary or acquired because of pulmonary, cardiac, gastrointestinal or other diseases. Clubbing may take years to develop or come on in a week. It may disappear if the primary disease is cured. Hypertrophic osteoarthropathy is an extension of the process of clubbing to more proximal parts of extremities and may develop in any condition capable of producing clubbing. Chief pathologic reactions are tissue hypertrophy and hyperplasia with the development of ossifying periostitis. But in the original bone, osteoclasia and resorption of bone may occur (Mendlowitz). Marked atrophy of terminal phalanges occurred in two cases of osteoarthropathy with clubbing (Weens and Brown).

Contrary to those who believe that clubbing is the initial phase, hypertrophic osteoarthropathy can occur without clubbing: a case was noted (Shapiro¹⁵⁹²). Because of articular symptoms an erroneous diagnosis of rheumatoid arthritis is often made.¹¹⁷³

The fundamental cause is unknown but increased peripheral blood flow appears to be a chief factor.¹²¹⁶ Hypertrophic osteoarthropathy was produced experimentally in a dog by anastomosis of pulmonary artery to left auricle causing an increased cardiac output.¹²¹⁷ Present in current cases of hypertrophic osteoarthropathy were pulmonary neoplasms,^{614, 1172, 1173, 1592} tetralogy of Fallot¹⁰⁰¹ or postoperative myxedema and progressive exophthalmos (third such case recorded).¹⁵²³ In one case articular symptoms disappeared immediately after removal of a fibrosarcoma of lung.¹¹⁷²

Fried⁶¹⁴ reported four cases of pulmonary osteoarthropathy with bronchogenic cancer; clinical and necropsy findings led him to believe that the lung disease produced dyspituitarism which in turn produced the osteoarthropathy and that the latter condition "may not be remote" from aeromegaly. A case previously diagnosed as hypofunction of pituitary secondary to aeromegaly was considered by Bernard as one of multiple ossifying periostitis with hypothyroidism. A case of pulmonary osteoarthropathy in a dog with pulmonary tumor was noted.¹⁹⁵⁴

Intrapelvic Protrusion of Acetabulum (Otto Pelvis). For intrapelvic protrusion of the acetabulum, Ghormley⁶³⁹ recommended cup arthroplasty when possible, arthrodesis only when necessary. Acetabuloplasty was not successful.⁶³⁹

Congenital Anomalies. 1. *Congenital Ankylosis of Elbow.* This condition (congenital humeroradial synostosis) is a rare abnormality of which only 24 cases have been reported.^{587, 616} Seven new cases were reported, one in a new-born babe (Murphy and Hanson¹²⁷⁶). Of Frostad's five cases,⁶¹⁶ three occurred in one family, two in another. Four relatives of Frankel's patient⁵⁸⁷ were similarly affected. Elbow spaces are still absent in the 22 mm. embryo; a dominant genetic anomaly results in continued complete absence of any elbow joint. In three of the four relatives of Frankel's patient⁵⁸⁷ patellae were absent or rudimentary. Victims seem liable to fatal chronic nephritis.

2. *Hereditary Triad: Arthrodysplasia of Elbows, Absence of Patellae, and Dystrophy of Nails.* This results from an inherited congenital development defect of ectodermal and mesodermal layers of the embryo. Nails, especially of thumbs, are absent or thin. Patellae are absent or markedly hypoplastic. Elbows show prominent internal condyles, increased carrying angle, elongation and deformity with luxation of the proximal end of radius. Secondary osteoarthritic changes may occur. Thirty relatives of one patient were affected within four generations.¹⁵⁸²

3. *Aplasia of Interphalangeal Joints with Synostosis of Carpal and Tarsal Bones.*¹⁶²¹ Proximal phalangeal joints were rigid in the two cases noted, due to absence of joints from hypoplasia or aplasia. Other skeletal anomalies were present.

4. *Hereditary Malformation of Hands and Feet.* Fifteen members of one family within four generations presented a defect which was expressed variably from lobster claw and split foot to long thumbs or absent nails (Stiles and Pickard¹⁷²⁴).

TENOSYNOVITIS

General Comments. Reviews of the types of tenosynovitis, symptoms and current ideas on etiology and treatment appeared.^{1112, 1442} Series of 190¹¹¹² and of 70 cases¹⁴¹² were analyzed. Types listed by Lipscomb¹¹¹² included: (1) acute infectious forms due to pyogenic infections or gonorrhea; (2) acute non-infectious forms due to gout or trauma; (3) chronic specific infectious forms due to tuberculosis or syphilis; (4) chronic nonspecific infectious form in which no definite infectious agent is known but in which the pathologic reactions "resemble those seen in chronic infectious [rheumatoid] arthritis," and (5) chronic nonspecific forms, crepitating, noncrepitating or stenosing. Contrary to previous opinions no type of chronic tenosynovitis was considered to be "rheumatic" (Reed and Harcourt^{1112, 1442}). Regardless of location, the presence or absence of crepitation or stenosis, Lipscomb¹¹¹² considered trauma to be the usual cause and stated: "the various pathologic changes differ only in degree and depend primarily on the duration of the disease." Crepitation may or may not be present in any type of tenosynovitis and is by no means constantly present, even in so-called crepitating tendovaginitis.

Pathologic reactions in 16 cases were described: tendons were normal; tendon sheaths or peritendinous tissues (if sheaths were absent) were affected by serous effusions with clumps of fibrin, sometimes by proliferation of synovial linings with villous formation, occasionally by myxomatous degeneration or marked fibrosis with collections of hemosiderin.

Results of various treatments were analyzed. Currently favored was a program of "conservative treatment" of 20¹⁴⁴² or 60 days,¹¹¹² with surgical exploration, if necessary, afterward (excision or incision of tendon sheath). Physical therapy alone gave poor results; roentgen therapy was slightly superior to surgical procedures.¹¹¹²

Tenosynovitis, Tendinitis and Peritendinitis among Military Personnel. Traumatic tenosynovitis, although relatively mild, rendered large numbers of soldiers non-effective for duty. Of 63 cases among soldiers studied by Volk the Achilles tendon was affected in 42 (67 per cent), the extensor hallucis longus in nine, the tibialis anticus in five, other tendons in seven cases. Achilles tendinitis appeared "in almost epidemic form, early in the training period, usually after initial hikes." Some believe that neither the synovial membrane nor the tendon is involved, but peritendinitis is present, the tendinomuscular junction being affected.¹⁸⁵⁶ Relief resulted after a few days of hot foot soaks and rest.

Johnson⁹¹⁶ described a painful swelling over a tendon (usually Achilles, tibialis anticus or flexor tendon of the hallux) situated at a point of pressure such as a fold in the leather of a boot. If irritation continued, the localized swelling was transformed into a circumscribed elevated nodule closely adherent to the skin. However, it could be lifted off the tendon. Sometimes two nodules were present with a tender groove between. Biopsies showed avascular fibrous tissue with few inflammatory cells; tendon and sheaths were normal. Correction of boots gave relief.

Acute and chronic suprapatellar, sometimes infrapatellar, tenosynovitis and fasciitis affected certain pilots of heavy bombers whose leg muscles were in constant tense contraction for four to nine hours from pressing against the rudder during long flights. A stiff-legged, waddling gait and broad stance developed. Strapping the patella upward relaxed the affected tendon and gave immediate relief (Conway).

Tenosynovitis of Long Head of Biceps. This is usually caused by a sudden jar or pull. Pathognomonic are pain and tenderness along the bicipital groove. Much benefit and occasionally instant cure result from sudden traction on the arm and shoulder while the arm is relaxed and abducted; presumably the tendon is replaced in an improperly fitting groove.¹¹¹²

"Snapping Thumb." This results from a lesion of the flexor pollicis longus tendon or sheath and is probably similar to stenosing tendovaginitis of the radial styloid.¹¹¹² Two infants had stenosing tendovaginitis of a thumb. A striking feature was flexion deformity of the interphalangeal (distal) joint. Injury had occurred in one case, not in the other. Surgical splitting of the narrowed sheath, "the only treatment of value," was successful. Zadek¹⁹⁸⁸ stated that "trigger-finger" implies a "snapping" but this was not present in either of these infantile cases.

"Snapping (Trigger) Finger." This results from chronic occupational trauma. Like a "snapping thumb" it is caused by a stenosing tendovaginitis of a flexor tendon sheath at the metacarpophalangeal joint in the palm (Wood). Either narrowing of the sheath or enlargement of the tendon prevents free passage of the latter (Lipscomb¹¹¹²). The reaction may be in tendon, not in the sheath; nodules may be found in the flexor pollicis longus tendon.¹¹¹² Surgical correction was advised.

Crepitating Tenosynovitis (Peritendinitis). This may result from prolonged exertion of unaccustomed muscular effort. The primary lesion occurs in muscles ac-

cording to some, in tendons according to most. Roentgen therapy was preferred by some.¹¹¹²

"Chronic Nonspecific Infectious Tenosynovitis." Marked cellular reaction (lymphocytes and plasma cells) "resembling that seen in arthritic tenosynovitis" was noted in one case.¹¹¹²

Stenosing Tendovaginitis at Radial Styloid (De Quervain's Disease). About 250 cases of stenosing tendovaginitis at the styloid process of the radius have been reported.¹¹¹² It affects chiefly women over 25 years old and occurred often in ex-office workers or ex-housewives who worked in war plants.^{10, 1213} This type of stenosing tendovaginitis is identical with that which produces "trigger fingers" or "snapping thumb" (Meadoff and Gray). Clinical features, pathology and pathogenesis in 46 cases were reviewed.^{10, 1112, 1213, 1344, 1405} Symptoms are produced by thickening of the fibrous sheath that covers the tendons and the synovial sheaths of the abductor pollicis longus and the extensor pollicis brevis as they pass through the bony groove in the radial styloid. A positive Finkelstein test is pathognomonic^{10, 1405}: the thumb is placed in the palm of the hand and grasped by the remaining fingers. With the hand in this position even slight forced ulnar deviation at the wrist will produce excruciating pain. Surgical treatment is simple and "uniformly successful."

Tenosynovitis of "Baseball-Finger." The lesion of a "baseball-finger" may involve tenosynovitis as well as traumatic osteoarthritis. Rupture of tendon at the insertion of the extensor expansion into the distal phalanx of a digit may produce a "drop finger" with loss of extension at the distal joint (Wood).

Peritendinitis Calcareo (Calcareous Tendinitis). The exact locations of calcific deposits near joints has been disputed. The older view was that they were mostly in juxta-articular bursae, hence such terms as "calcific bursitis." On the basis of surgical dissections others (notably Codman, 1934) consider them practically always primarily within tendons and only secondarily, if at all, in bursae; hence, the term "calcific tendinitis."⁹¹⁸ According to Sandstrom whose work (1937-1938) is credited with bringing some order out of chaos, the deposits may be in tendons or tendon sheaths, in peritendinous tissue, ligaments or articular capsule; hence he considered the inclusive term "peritendinitis calcarea" more accurate. His view and term have been widely accepted,^{373, 910} although some prefer such terms as "para-arthritis"⁵⁸⁴ or "para-articular calcification."¹²⁸⁷ Thus many now consider calcific subdeltoid, trochanteric or radiohumeral "bursitis" to represent, not bursitis, but peritendinitis calcarea.^{373, 917} Even Pellegrini-Stieda disease is regarded by some as a calcifying tendinitis.^{19, 182, 210, 584, 1287}

Sites most commonly affected are shoulders, elbows, hips and knees; less often wrists, fingers, ankles, metatarsals. Of Frank's 14 cases⁵⁵¹ an elbow was affected in five, knee in four, hip in two, shoulder in one, hip and shoulder in one, wrist in one. Cases may be acute, chronic or latent (symptomless calcifications seen in roentgenograms). Acute or chronic microtrauma presumably damages the tendon with resultant decreased vascularity, necrosis of fibrous tissue, secondary calcification and in some cases even ossification.^{373, 584, 910} The pathologic reaction was described⁹⁴⁵ and illustrated.³⁷³ To find certain deposits roentgenograms taken in special positions may be required.

1. *Shoulders.* These will be discussed under "Diseases about the Shoulder."

2. *Hips.* Calcific tendinitis may occur near the greater or smaller trochanter or close to the upper acetabular rim. Forty cases were discussed.^{551, 948, 1092} Careful dif-

ferentiation from os acetabuli, sesamoids and capsular calcifications may be necessary; roentgenographic differentiation was nicely described by Zander.

3. *Fingers.* Calcareous tendinitis in fingers is "extremely rare." Ten cases were reported (Cooper; Zander³⁷³).

4. *Wrist.* The site commonly affected is "at the pisiform, probably in the tendon of the flexor carpi ulnaris."^{373, 584}

5. *Elbow.* One case was reported.⁵⁸⁴

6. *Knees.* Some^{182, 584, 947} who presented cases of "calcific tendinitis" or of "peritendinitis calcarea" at the mesial aspect considered this condition as equivalent to Pellegrini-Stieda disease. But according to others Pellegrini-Stieda disease is not a calcific tendinitis but is a calcific ligamentitis^{19, 1287} or ossifying epiperiosteal hematoma.¹⁰⁸³ The relationships will be discussed under "Miscellaneous Conditions."

7. *General Treatment.* Of the various treatments discussed Frank⁵⁸⁴ preferred rest and immobilization in acute cases, roentgen therapy in chronic cases. Roentgen therapy was favored by Zander¹⁰⁹²: in a case with both hips affected the symptoms and calcific deposits disappeared rapidly from the radiated side and remained unchanged on the untreated side. Immobilization in plaster or splints for five to seven days, then physical therapy for one to three weeks cured Cooper's 78 patients.³⁷³ According to Kaplan⁹⁴⁷ rapid relief was afforded by procaine.

DISEASES OF BURSAE

New anatomic studies were made.

Five bursae, hitherto undescribed, were located deep to the tibial collateral ligament (Brantigan and Voshell). Adventitious bursae are not present at birth but are acquired probably as a result of repeated trauma to soft tissue over a bony prominence. They develop as do normal bursae: connective tissue condenses and a fluid-containing cavity appears as a result of mucoid or myxomatous degeneration of connective tissue. Adventitious bursae, unlike true bursae, have no endothelial or other real lining. They are subject to the same diseases as true bursae: infection; enlargement; tumors; fibrosis.^{242, 1045}

Etiologic Classification. A provisional etiologic classification was offered by Cherry and Ghormley. Among 41 bursae removed surgically, eight diseases were found. The only specific infection noted was tuberculosis. Tuberculosis usually affects larger bursae around large joints but tuberculous bursitis of a toe was noted.³¹² Bursitis lateral to a greater trochanter is rare; when present it is often due to tuberculosis secondary to that of the trochanter (Donovan and Sosman).

Various Bursae: Clinical Data and Treatment. 1. *Shoulder.* Bursitis about shoulders will be discussed in the next section.

2. *Elbow.* An acute calcified bursitis near the lateral epicondyle of a humerus responded rapidly to roentgen therapy and diathermy. Absorption of calcium occurred (Young¹⁹⁸⁰).

3. *Groin.* Cystic tumor of the iliopectineal bursa was seen in two cases, in one of which the tumor later connected with an arthritic hip (Stephens).

4. *Hip.* Tuberculous bursitis⁴⁷⁷ was present in five cases; severe acute calcified trochanteric bursitis secondary to calcific tendinitis of the gluteus medius in seven.¹⁵⁵⁰

In the latter cases fever, acute disability occurred for a few days only, then rapid recovery on rest in bed, applications of heat or cold, injections of procaine.

5. *Knee.* Ossification of an infrapatellar bursa and fat pad ("an osteoma") was relieved by surgical excision.¹⁴⁷⁵ In 10 cases "a new entity," noncalcific bursitis beneath the tibial collateral ligament, was treated successfully by procaine or excision (Voshell and Brantigan). Calcification of the most superior of the five newly discovered bursae deep to the tibial collateral ligament may account for *some* cases of Pellegrini-Stieda disease.²⁰⁷

The important bursae of the popliteal space may communicate with each other or with the joint. Communications with the joint are often open when the knee is extended, closed when the knee is flexed. The part these bursae play in the production of "Baker's cysts" is not agreed on (see "Synovial Cysts of Popliteal Space").

A case of traumatic degeneration of the medial head of the gastrocnemius simulating semimembranosus bursitis was recorded³¹⁸; also one of osteochondromatosis of a popliteal bursa.¹⁹⁸⁹

6. *Heel.* Inflammation of the posterior calcaneal bursa was common in the infantry. Retrocalcaneal bursitis was differentiated from Achilles tendinitis. Successful ambulatory treatment consisted of the application of cylinders of cotton behind malleoli, held in place by adhesive.⁴⁴⁴

7. *Multiple Sites.* A boy and two siblings presented large multiple calcified bursae in gluteal regions, an elbow, a foot. Studies on calcium balance were negative. Treatment was removal of bursae and the continued daily oral use of sodium citrate.⁶¹⁶

General Treatment. Usually recommended were sulfonamides³¹² [or penicillin—Ed.] for acute bacterial bursitis, drainage for acute suppurative bursitis,³¹² excision for tuberculous or xanthomatous bursitis,^{312, 477} single or repeated aspirations by some³¹² or conservative nonsurgical treatment by the majority for acute traumatic bursitis. Roentgen therapy gave excellent results in cases of non-specific, noninfectious bursitis, acute or chronic, calcific or noncalcific.^{1101, 1080}

Hyperemia induces healing in acute or chronic nonspecific calcific bursitis: "anything causing increased vascularity causes absorption of the calcific deposit and cure." The inflammation which accompanies acute bursitis produces a curative hyperemia during which calcific deposits often resorb. According to Schein and Lehmann¹⁵⁵⁰ diathermy, static brush discharge, roentgen therapy, local applications of heat or cold, injections of procaine, aspiration of calcific material produce an increase in local hyperemia and the same general result with varying rapidity.

For chronic traumatic bursitis, so often not relieved by slow conservative methods, Burgess devised a "seniconservative procedure—simple paracentesis and internal bursotomy of the bursal sac creating a new communication between the sac and the adjacent subcutaneous tissue." Results were successful in 14 cases of chronic traumatic prepatellar or olecranon bursitis. It involved no time loss or disability for workmen.

Sclerosing solutions have not been widely used; too often they aggravate the bursitis without obliterating the sac.²⁵⁵ An improved method was used by Cottrell: injections of sclerosing agents plus the use of a special type of rubber drain. Of 27 patients with chronic (olecranon, patellar or popliteal) bursitis with effusion so treated, 25 were rapidly cured. For chronic nonspecific bursitis not relieved by conservative means Cherry and Ghornley recommended surgical removal.

DISEASES ABOUT THE SHOULDER JOINT: THE PAINFUL SHOULDER

Anatomy and Function. An improved knowledge of the normal function of the shoulder should lead to better diagnosis and treatment of its diseases. To this end the motions and functions of the shoulder of man and animals were studied by electromyograms (Inman, Saunders and Abbott) and by the fluoroscope (Fisk). Past writings have so stressed the motion of the scapulohumeral joint as to infer that movements of scapula, clavicle and sternum are of little importance. According to Fisk 50 per cent of the motion of the shoulder concerns the scapula and clavicle: "The scapulohumeral joint is responsible for only half the movement at the shoulder"; the range of motion at this joint is much more limited than is commonly supposed. The "shoulder joint" actually consists of four independent joints: the sternoclavicular, acromioclavicular, scapulothoracic and glenohumeral: shoulder motion is "the sum of movement contributed by synchronous participation of all these joint units."⁸⁹⁵ Complete elevation of the arm depends on free motion of all these joints. "The old teaching that abduction to the right angle takes place entirely at the glenohumeral joint, and that thereafter, full elevation is completed by motion of scapula on the chest wall, is incorrect." On the contrary, motion occurs simultaneously in all joints of the region, each contributing its share. During early phases of elevation of arm, the sternoclavicular joint passes through its greatest range of motion; in the terminal phase, the acromioclavicular. "At the glenohumeral and scapulothoracic articulations, the ratio from almost the beginning to the termination of the arc, is respectively two to one, so that for every 15 degrees of elevation the glenohumeral contributes 10, the scapulothoracic 5 degrees." Ankylosis of any of the joints causes a permanent loss in degree of movement in direct proportion to the amount of movement that joint should have contributed.⁸⁹⁵

Terminology. More confusion appears to surround the subject of "painful shoulder" than any other topic in this Review. In current writings there is little harmony of thought among either physicians or orthopedists.

Terms used in 40 recent papers truly reflected "Babylonian confusion."¹⁷⁷⁵ In general, four main topics were discussed: calcific tendinitis or bursitis or both, noncalcific tendinitis or bursitis, tears of the musculotendinous cuff, and the "frozen shoulder" considered by some^{1110, 1111, 1775} synonymous with "periarthrititis." But these terms and the symptomatology diagnostic thereof were by no means clearly defined. Take, for example, the term "frozen shoulder." According to some writers this condition (a painful shoulder with motion limited in all directions and usually with no calcific deposits) is always, or almost always, caused by one lesion but there was no agreement on the lesion. It is (generally) caused by "adhesive capsulitis" (noncalcific synovitis and bursitis) according to one,¹²⁹⁷ by adhesive or obliterative subdeltoid bursitis according to others,^{188, 310, 1206} by tenosynovitis of the long biceps tendon,^{876, 1110, 1111} by acute calcific bursitis secondary to calcific tendinitis of one of the rotator muscles, generally the supraspinatus,¹⁸² by "fibrositis"¹³⁰² or idiopathic myalgia especially of the serratus posterior superior¹⁸¹² according to others. Others believed that several different pathologic lesions can produce the clinical picture identified as the "frozen shoulder."^{182, 1207, 1775, 1935} They included: acute subdeltoid bursitis, "humeroscapular bursitis," chronic adhesive bursitis, calcific supraspinatus tendinitis, rupture of supraspinatus tendon, peritendinous and pericapsular adhesions ("adhesive capsulitis"), "interstitial fibrosis," bicipital tenosynovitis, "arthritis of shoulder joint."^{182, 1206, 1207, 1297, 1775}

Some used the term "subdeltoid bursitis" with anatomic specificity; others as a general term under which they discussed a variety of lesions.^{57, 182, 1205}

One writer stated¹²⁰⁵ that it is fashionable but incorrect to label most sore shoulders as "bursitis." To add to the confusion one writer used the term "supraspinatus syndrome" (in contrast to "supraspinatus tendinitis") to include a variety of lesions not of the supraspinatus tendon.¹⁸⁸

Space does not permit analysis of what each writer meant by the terms used. Reading of a representative number of articles is suggested.^{57, 182, 186, 188, 876, 921, 1110, 1111, 1206, 1207, 1322, 1775, 1935}

[Until terminology is less confused and the differential diagnosis of the lesions which produce "the painful shoulder" is better understood it would be well to adopt Bosworth's suggestion¹⁸⁸ that since a precise preoperative diagnosis often cannot be made, the clinical diagnosis should be given in two parts: (1) "internal derangement of the shoulder"; (2) the name of the lesion suspected but not certainly present as "internal derangement of shoulder: noncalcific supraspinatus tendinitis." We consider this a more "honest" and much less confusing method of nomenclature than that currently used, and as Bosworth stated,¹⁸⁸ the term "internal derangement" should be as applicable to the shoulder as to the knee. But some of the lesions under discussion are external to the shoulder joint.—Ed.]

Relative Incidence. As to the commonest cause of shoulder disability and the relative incidence of the various lesions disagreement was marked even among surgeons. Each of the following was voted the most common cause of shoulder pain: bursitis¹²⁰⁵; rotator tendinitis¹⁸⁸; arthritis of acromioclavicular joint¹³²²; fibrositis of trapezius or adjacent muscle.⁹⁷⁴ In 58 shoulders explored by Bosworth¹⁸⁸ tendinous lesions were found in 43; bursal in eight; osseous in five; none in two despite symptoms suggesting supraspinatus tendinitis.

Calcium Deposits About Shoulder. The roentgenographic incidence of calcium deposits about the 12,122 shoulders of 6,061 unselected persons "of the white collar class" undergoing periodic examinations was noted by Bosworth.¹⁸⁶ Calcium deposits were found in 165 (2.7 per cent) persons, in 202 shoulders. Males were affected more often than females; women typists more often than women clerks; right shoulders twice as often as left. Values for blood calcium were normal. The incidence of the deposits rose up to the age of 50 years. Many persons had bilateral deposits. Multiple deposits occurred in 20 per cent of affected shoulders: 51.5 per cent of involved shoulders had deposits in supraspinatus tendon, 44.5 in infraspinatus tendon, 23.3 in teres minor. Only five shoulders showed calcium in the subscapularis. Calcium was visible in the subacromial bursa in 25 shoulders.

The four short rotator tendons are the subscapularis anteriorly, the supraspinatus and infraspinatus above, and the teres minor posteriorly.¹⁹⁰ But as these tendons become indistinguishably fused to form the capsule of the shoulder joint (conjoined tendon or musculotendinous cuff), it is difficult to determine which tendon contains the deposit. Bosworth¹⁹⁰ located them by fluoroscopy and by noting "the rotation of the arm which brings the deposit in profile." But Baird⁵⁷ considered it impossible in most cases to determine the exact anatomic location of these deposits roentgenographically. According to Howorth⁸⁷⁶ supraspinatus calcifications are located just above the junction of the greater tuberosity and head of humerus; those of infraspinatus and teres minor are lower and superimposed on the tuberosity except in

internal rotation; those of subscapularis are superimposed on the joint in internal rotation, on the head in external rotation. Of Howorth's 100 patients⁸⁷⁶ 40 per cent were men, 60 per cent women; most of these deposits affected the supraspinatus, "several" the infraspinatus or teres minor, only one the subscapularis.

In explored shoulders the deposits were rarely located in the bursa alone; almost always in the supraspinatus tendon which forms the floor of the subdeltoid bursa.^{876, 923, 1205} The general opinion was that the deposits are primarily in the tendon and may rupture into the overlying subdeltoid bursa. Many small deposits disappear without symptoms; cases of silent or quiescent calcific tendinitis are numerous. But in Bosworth's¹⁹⁰ experience "large deposits always result in a painful shoulder sooner or later, though they may remain quiescent or symptomless for months or years." Of 202 affected shoulders which Bosworth¹⁹⁰ followed for three years 132 (65 per cent) were painless, 70 (35 per cent) became painful, 18 acutely, 52 "mildly" or "slightly."

The exact relationship between calcium deposits and acute attacks was disputed. In general the size, number or location of deposits was not proportional to symptoms and signs of disability.^{57, 876} According to most writers, the degenerative changes and calcium deposits in avascular tendons are symptomless; only when calcium ruptures into vascular peritendinous tissue does inflammation occur; when it ruptures from the supraspinatus tendon into the overlying subdeltoid bursa, acute chemical bursitis occurs.^{57, 182, 190, 1206, 1935} However, according to Howorth⁸⁷⁶ acute attacks are not due to rupture of tendinous calcific deposits into bursae but to the increased tension produced in the tendon; when the deposit ruptures into bursa "immediate relief" occurs.

Lesions of Individual Tendons. Any of the five tendons of the shoulder (the four rotators and the long head of the biceps tendon) may be affected by (1) degenerative tendinitis without calcification, (2) calcific tendinitis, or (3) partial or complete rupture. The supraspinatus was most often affected.

The causes of tendinitis (acute or chronic, calcific or noncalcific) are not precisely known. No relation to focal or systemic infection has been proved; cultures of affected tendons and adjacent bursae have been negative.^{186, 405, 876, 1935} The tendinitis bears no relation to arthritis or rheumatic diseases.¹⁸⁶ Deficiencies of vitamin C¹⁹³⁵ or E¹⁷⁴⁹ or an endocrine disturbance have been suggested but not proved.^{485, 1516} Repeated exogenous trauma is not a proved cause^{57, 190} and according to some¹⁹⁰ single acute direct trauma practically never damages rotator tendons. Endogenous trauma was generally regarded as the main cause of the tendinitis; occupational trauma related to abduction and twisting^{57, 190, 465} produces attrition and "use-destruction."³¹⁰ Microscopic tears lead to degeneration and necrosis.^{57, 870, 1206} If tendons are affected by fatty degeneration, saponification and precipitation of calcium carbonate result in "calcific tendinitis." But if hyaline degeneration occurs, no saponification or calcium deposition results and the reaction in tendon (or associated bursa) is serous: serous exudate; precipitation of fibrin; formation of loose adhesions caused by fibrin rather than fixed adhesions from fibrous tissue.¹⁸² Quiescent calcific tendon lesions are supposedly "those in which the deposit is buried deeply enough in tendon tissue so that no peritendinous (bursal floor) irritation takes place."¹²⁰⁶

Bicipital (noncalcific) tenosynovitis is the commonest cause of "frozen shoulder" according to Lippmann^{1110, 1111}; it was present in 26 of 30 cases. The symptoms, pathology and pathogenesis of bicipital tenosynovitis were reviewed. "Spontaneous cure inevitably results" when the tendon fuses to the bicipital groove after three months to two and one-half years. Conservative treatment is justified unless a rapid cure is desired; the latter is accomplished by suturing the tendon to the lesser tuberosity. Despite the appearance of a "frozen shoulder" no true contracture of articular capsule is present as surgical release of the tendon immediately restores full motion of shoulder.

Supraspinatus tendons may be affected by calcification and ossification or laceration.¹⁸⁸

Among unselected cadavers studied by Jones⁹²¹ lesions of supraspinatus tendon were present in 30 to 40 per cent; large complete ruptures in 15 to 20 per cent. In a study of cadavers Wilson and Duff found complete rupture of supraspinatus tendon in 22 per cent, partial rupture in 20 per cent, rupture of bicipital tendon always secondary to that of the supraspinatus in 7 per cent. A normal supraspinatus tendon does not rupture; degeneration must occur before traumatic rupture occurs (Wilson¹⁹³⁵). Calcific deposits are rarely present in ruptured tendons (Baird⁵⁷). Symptoms, signs and roentgenographic features of ruptured tendons were discussed; treatment involves operative repair.^{57, 188, 876, 1935, 1936}

Lesions of Conjoined Tendon. Lesions of the musculotendinous cuff produce symptoms much like those of other lesions just described. The nature, location, symptoms of complete and incomplete tears and treatment were discussed.^{100, 1205, 1297} Neviaser regarded adhesive capsulitis as the chief cause of frozen shoulder and recommended manipulation under anesthesia.

Lesions of Bursa. It is accepted that the subdeltoid and subacromial bursae are "one and the same": when the arm is abducted the entire bursa is subacromial; when it is adducted much of the bursa is subdeltoid.⁹²³ According to most writers subdeltoid bursitis, calcific or noncalcific, is never a primary entity but always secondary to some lesion near by, generally in the supraspinatus tendon (tendinitis, tear or calcific deposit) which forms its floor.^{713, 1035} McLaughlin¹²⁰⁵ went a step further and stated that when subdeltoid bursitis is present "it usually constitutes a second condition having no connection with the primary lesion other than proximity." Subdeltoid bursitis is the "inevitable result" of calcific tendinitis, according to Bosworth.¹⁰⁰ Most writers supported Codman's (1934) view that calcific deposits are practically never in the bursa but in the tendon beneath^{923, 1205}; Howorth⁸⁷⁶ found calcium in only one of 23 bursae explored but Baird noted one bursa "completely filled" with calcium. Pathologic reactions in bursae were described.^{463, 876} The bursitis may be serous (noncalcific) or calcific⁹⁸²; acute, subacute, chronic or quiescent. Laceration of bursal floor without involvement of tendon occasionally occurs.¹⁸⁸ "Subacromial bursitis" may be secondary to, or associated with a disorder of the central nervous system, according to Dynes.

Treatment of Tendinitis and Bursitis. 1. General Comments. Physicians wrote mostly about the treatment of calcific tendinitis and bursitis, less about ruptures and little about other noncalcific lesions. Distinctions between the treatment of calcific and noncalcific inflammations were poorly made: remedies for both were about the same except that for calcific lesions physicians, especially orthopedists, revealed an almost unconquerable urge to remove the calcium. Tears of tendons or cuffs were usually treated by surgical repair.

The following pertains to calcific tendinitis and bursitis. Calcium deposition in tendons is a reversible process; unless they are large the deposits are generally absorbed by any process involving acute hyperemia. The mechanics of precipitation and resorption of calcium were discussed.¹⁹³⁵ Even an acute inflammatory reaction itself carries with it the mechanism for calcium absorption. This is why so many deposits disappear rather rapidly after almost any treatment for the acute attack or even with none. Therefore conservative measures were recommended in most acute cases. Surgical measures were reserved for chronic conditions unrelieved by conservative measures or for acute cases in which resolution and healing appear tardily or "a rapid cure" is desired. No remedy was successful in all cases: 50 per cent of patients were readily relieved by this or that remedy. Results of almost any measure were good in acute cases, often disappointing in chronic cases.^{57, 188}

2. *Conservative Measures.* Physical therapy was considered of real value by some,^{124, 500} of use only as an adjuvant,^{186, 465, 876} or usually unsatisfactory.³¹⁰ Calcium deposits are only affected by long wave diathermy according to Echtman.⁵⁰⁰ Solomon and Morton¹⁶⁷³ regarded diathermy as useful as roentgen therapy. Sometimes cold was preferred to hot applications which may occasionally aggravate symptoms.⁸⁷⁶ Prolonged physical therapy may be more expensive and less suitable than other measures including surgery.¹⁸⁶ Immobilization by splints and plaster during acute attacks was condemned: it fosters formation of adhesions and stiffness.^{186, 876, 1935} Manipulation under anesthesia may be "disastrous" (Howorth⁸⁷⁶). Ammonium chloride given orally to hasten absorption of calcium gave results in five cases of calcific supraspinatus tendinitis satisfactory to Dick, Hunt and Ferry.⁴⁶⁵ Results of intravenous injections of iron cacodylate given by Pelner¹³⁶² were negative in calcific bursitis, presumably "spectacular" in noncalcific subdeltoid bursitis. Synthetic vitamin E (alpha tocopherol) was valueless¹⁷⁴⁹; neostigmine useful.^{938, 1815}

Roentgen therapy was the most favored conservative measure and was considered by most writers to be satisfactory in cases of acute or chronic calcific or noncalcific tendinitis or bursitis.^{57, 310, 774, 923, 1401, 1980} Sometimes symptoms rapidly subsided and calcium deposits disappeared.^{57, 182, 923, 1515} Results were best in acute cases or in chronic cases in which the deposits were soft, fuzzy and small, less notable in chronic cases or in acute cases with large, dense, discrete deposits.^{182, 876} Roentgen therapy dilates capillaries, increases their permeability, leads to phagocytosis of fibrin and necrotic tissue. The effect is not a direct one on the deposits; it does not affect quiescent calcific deposits (Borak¹⁸²).

3. *Surgical Measures.* Each of the following remedies received enthusiastic support and apparently gave excellent results especially in acute cases. Injections of procaine relieved acute subacromial bursitis without calcification.⁷¹³ Simple needling and infiltration of calcific tendons or bursae with saline promptly cured other acute cases.^{947, 1065} Multiple needling, or needling and aspiration of calcific material was used successfully by some¹²⁰⁶ but not by others.^{876, 947} Irrigation of acutely inflamed bursae by means of two needles for inflow and outflow was approved by some^{982, 1345} but considered difficult, unsatisfactory and less helpful than surgical excision by others.^{190, 876, 1935} Block anesthesia and manipulation were used by Tarsy.¹⁷⁷⁵

For acute calcific tendinitis or the "acute supraspinatus syndrome" operative drainage, incision of tendons and excision of necrotic calcific material were considered best by several workers^{186, 713, 876, 1206, 1935}: Average hospital stay is only four days and "immediate, certain, complete and permanent relief" results (Bosworth¹⁸⁶). "There are only two forms of therapy simulating nature's method of cure (extrusion of calcium from tendon) and having proved curative effects, opening of the deposit by knife or needle" (McLaughlin¹²⁰⁶).

For acute posttraumatic noncalcific lesions of shoulder unrelieved by one or two weeks of conservative therapy or for intractable chronic cases surgical exploration was recommended: in such cases unsuspected tears and other lesions amenable to surgical repair are often found.^{921, 1206}

Lesions of Joints. Rheumatoid or osteoarthritis of acromioclavicular joint was regarded by Oppenheimer^{1320, 1322} as a more common cause of painful shoulder than heretofore suspected. For it he recommended roentgen therapy. In the "frozen

shoulder" the synovia and cartilage of the joint are not affected.¹⁸² But no articular lesion was found responsible for any of Bosworth's 53 cases of painful shoulder. A case of posttraumatic pericapsular ossification and ankylosis was noted.⁷⁰⁷

Lesions of Muscles. Fibrositis of trapezius or adjacent muscles, or "idiopathic myalgia" of muscles of back and shoulder, especially of the serratus posterior superior muscle were considered common causes of "painful shoulders."^{1302, 1812} Procaine infiltration of tender spots was recommended.

Lesions of Bone. Irregular destruction and cystic lesions of the humeral head may be associated with severe or chronic tendinous lesions. Among Bosworth's cases¹⁸⁸ of "supraspinatus syndrome" were two of humeral osteochondritis.

"The Shoulder-Hand Syndrome." As a complication of about 10 or 20 per cent of cases of coronary occlusion, less often angina pectoris, shoulders may be affected by pain alone or by painful stiffness (Howard, 1930; Eideken and Wolferth, 1936; Ernstene and Kinell, 1940). Sometimes a hand is affected: "the shoulder-hand syndrome."¹³⁰²

In Askey's 22 cases of the latter, pain and stiffness affected generally a shoulder one week to seven months after coronary occlusion or angina; a few weeks later a hand was affected becoming painful, stiff and swollen with tense glossy discolored skin and markedly limited motion simulating sclerodactylia. The whole hand was affected, not just joints. Palmar thickening resembling Dupuytren's contracture sometimes developed. Pain in shoulder or hand was severe, at times requiring narcotics. Pain affected a right shoulder and hand in 11 cases, left shoulder and hand in 10, both sides once. A consistent point of maximal tenderness corresponded to the site of trapezius branches of cervical plexus. Curiously pressure over this spot sometimes relieved pain temporarily, once permanently. The disability lasted several months to two years (average six months). Residual stiffness usually resulted.

Six to eight weeks after myocardial infarction hands and wrists were affected by "periarthrititis" in three cases of Meyer and Binswanger. Shoulders or hands or both were affected in 39 of 178 consecutive cases of myocardial infarction studied by Johnson⁹¹⁴ who termed the condition "post-infarction sclerodactylia." In these 39 cases "joints" became affected three to 16 weeks after the infarction. Pain, limited motion, atrophy and palmar contractures affected the hands. Johnson⁹¹⁴ considered the "periarthrititis" of shoulders to be unrelated to the disability of hands. At necropsy an affected shoulder in one case was entirely normal. Six cases of Dupuytren's contracture (four of painful stiff shoulders) after myocardial infarction were noted by Kehl.

Thirteen cases of painful shoulder with effort angina or myocardial infarction were noted by Travell, Rinzler and Herman.¹⁸¹² A "frozen shoulder" may also complicate pulmonary disease (Lippman¹¹¹⁰). [No data given.—Ed.] The relation of myalgia and arthralgia of the left shoulder to coronary disease was also discussed by Harrison. After hemiplegia or Parkinson's disease "subacromial bursitis" may develop, so stated Dynes. [In these cases the "bursitis" may have represented an incomplete "shoulder-hand syndrome."—Ed.]

Askey regarded the condition as "a combination of sympathetic nerve disturbance and arthritis." According to Johnson⁹¹⁴ the involvement of hand may result from "anoxia of the tissues of fingers produced chiefly by ischemia resulting from reflex vasoconstriction of arteries of hand induced by cardiac pain." An "irritation of sympathetics" was blamed by Kehl.

Various treatments given by Askey were valueless including salicylates and paravertebral injections of alcohol into first and second dorsal sympathetic ganglia.

[The "shoulder-hand syndrome" also may occur after hemiplegia, splinting of an arm after fracture, manipulation of a shoulder or "spontaneously." This phenomenon possibly may be related to the painful vasomotor disturbance, causalgia or Sudeck's bone atrophy even though the former is presumably related to ischemia and the latter to vasodilation.^{463, 464}—Ed.]

Miscellaneous Causes of Shoulder Pain. Various other causes of painful shoulders were noted: acute epidemic myalgia of neck and shoulders^{111, 112}; lesions of cervical spine—osteoarthritis, tuberculosis, malignancy, herniated disks^{355, 749, 1237}; scalenus anticus syndrome,⁹³⁵ cervical rib,⁴²² and other neurologic lesions.^{1683, 1975}

DISEASES OF MUSCLES AND FIBROUS TISSUE

Diseases Caused by Trauma. 1. *Traumatic Myositis.* The mechanism of injury, diagnostic features, pathology and treatment of muscular injuries, particularly in athletes, were reported (Northway). Under the term "traumatic myalgia" Good⁶⁷⁴ discussed what others would have called "fibrositis related to trauma."

2. *Traumatic Myositis Ossificans.* This type of myositis ossificans is more common in the brachialis muscle than elsewhere in the body; it is usually a late complication of posterior dislocation of the elbow (Loomis¹¹²⁵). The relation of traumatic myositis ossificans to injuries of nerves was discussed: such cases, sometimes mistaken for bone sarcoma have led to "surgical disasters" as amputations (Brailsford²⁰⁴).

Myositis Ossificans Progressiva. Cases of the progressive, nontraumatic form of myositis ossificans were noted.^{1335, 1520, 1853} In 75 per cent of such cases a congenital anomaly is associated; an unusual case without such anomaly was reported (Ryan¹⁵²⁰). In one case the condition developed subsequent to disseminated congenital osteomas of skin¹⁸⁵³; in another it was associated with sarcoma in muscles overlying a scapula.¹³³⁵ In two cases osteogenic sarcoma developed in a pre-existing myositis ossificans circumscripta (Pack and Braund¹³³⁵).

Suppurative Myositis. Gonococci were recovered from a swollen left calf in a case of suppurative gonococcic myositis and arthritis.¹¹⁰⁷ A case of suppurative anaerobic streptococcic myositis⁷⁹⁹ and one of staphylococcic myositis¹⁸⁴⁴ were noted.

Tropical Myositis. This is an acute purulent or nonpurulent myositis common in the Eastern tropics: it is presumably identical with primary suppurative myositis as seen rarely in the United States. Neither the infecting germ nor the mode of its entry is constant. One or more microorganisms may be recovered, most often staphylococci, streptococci, colon bacilli or combinations of these. A case due to hemolytic streptococci was reported from North Carolina (Cockrell).

Myositis from Scurvy. In an outbreak of scurvy among prisoners in Kenya painful tender indurated swellings affected various muscles especially of the

calf; they resembled somewhat nonsuppurative tropical myositis (Wiseman¹⁹⁵³). Under therapy with vitamin C (lemons) symptoms disappeared and no new cases occurred.

Trichinosis: "Trichinal Rheumatism." The examination of 5,313 diaphragms from 189 hospitals in 37 states revealed an average incidence of diaphragmatic lesions of 16 per cent, exposure to trichinosis being nearly uniform regardless of geographical or environmental factors (Wright and Walton).

The clinical similarity between trichinosis and periarteritis nodosa may be so great that differentiation is impossible without microscopic evidence. In two cases regarded by Reimann, Price and Herbut as trichinosis, typical lesions of periarteritis nodosa were found in tissues during life. Present were symptoms of "trichinal rheumatism": painful shoulder and masseter muscles; recurrent arthritis; fever; periorbital edema; conjunctivitis; eosinophilia. In one case precipitin tests with *Trichinella* antigen were positive in high dilution but trichinellae were not found in muscles. In the other case painful muscles, acute arthritis of knees and ankles, and intramuscular encysted larvae were noted; biopsies revealed evidence of periarteritis nodosa before, but not after, death. "There is a possibility that trichinosis as a disease with strong allergic manifestations may in certain instances serve as one cause of the syndrome called periarteritis nodosa."

Epidemic Myositis or Myalgia. 1. Epidemic Pleurodynia; Bornholm Disease. Clinical features of Bornholm disease are high fever, prostration, pleural and abdominal pains; involvement of trapezius muscle is rare as are also widespread muscular symptoms. In recent epidemics there were unusual features. Among 166 cases in Brooklyn (1942), a high incidence of pharyngitis and meningoencephalitis was noted. Most of the affected children had convulsions⁸⁷³; 11 of 16 nurses had involvement of central nervous system.¹¹⁸⁸ Muscles around shoulder and neck were notably affected in Ronald's 12 cases, presumably from referred pain resulting from involvement of diaphragm or diaphragmatic pleura. Clinical and epidemiologic aspects in 75 cases occurring near Mobile were reported.¹³⁰⁰ Outbreaks affected military personnel.^{12, 1192}

2. Other Forms of Epidemic Myositis. A "hitherto undescribed form of epidemic myositis" was seen by Williams¹⁹²⁶ in five young recruits after inoculation with tetanus toxoid and T.A.B. vaccine. Myositis affecting abdomen, chest, shoulder, pelvic girdle and limbs developed with meningeal symptoms, neuritis and erythema.

[Could this not have been atypical epidemic pleurodynia with meningeal symptoms as noted in the preceding paragraph, the condition being only coincidentally related to the immunization therapy?—Ed.]

At present Bornholm disease is the only recognized form of epidemic myalgia. The common "stiff neck" or acute torticollis may represent another form of epidemic myalgia. An epidemic of "stiff neck" occurred in England in 1941: 125 cases were studied by Beeson and Scott.^{111, 112} Trapezius muscles were chiefly affected, sometimes deltoids and sternomastoid. Abdominal and pleural pains were absent. Symptoms resembled the common sporadic "stiff neck" of acute fibrositis. Most cases were mild and of short duration but occasionally the disease became chronic, involved other muscles and resembled generalized

fibrositis—cases which “would not ordinarily be identified as having originated from an epidemic of benign myalgia of the neck.” Transmission to human beings appeared to be accomplished through the agency of whole blood from acute cases. Perhaps cases of so-called sporadic acute fibrositis of neck sometimes represents an undetected epidemic.

A small epidemic of acute myalgia affected members of a nursing staff: one to three weeks after an acute sore throat seven nurses developed fever, pains in muscles of chest and extremities which persisted sometimes for five months. A myotropic virus was held responsible (Houghton and Jones).

During an epidemic of atypical poliomyelitis studied by Rosenow cases were seen which culminated “in a strange and painful disease or state” called “encephalomeningoradiculitis with fibromyositis”; streptococci in water supply were the suspected cause.

“*Myalgia*”; “*Myalgic Spots*.” The main objection to the concept of fibrositis is our lack of knowledge of its pathology (Collins³⁵⁸; Gordon⁶⁸²). It has been difficult to demonstrate it or to confirm the meager data of early workers (Buckley²⁴³; Stockman¹⁷³⁰). In the United States and to a lesser extent in Great Britain, “the home of fibrositis,” many physicians have hesitated to make a diagnosis of fibrositis or have used the term reluctantly and with dissatisfaction. Stimulated perhaps by the work of Kellgren (1938)¹¹ many writers are now discussing under the noncommittal term “myalgia” what they formerly would have called fibrositis. Instead of “fibrositic nodules” we now read of “myalgic spots,”^{377, 979, 1930} “tender spots,”^{423, 519} “trigger zones”¹⁶²³ or “trigger points.”¹⁸²⁹ These myalgic spots are to be zealously sought and injected with procaine with the expected relief of referred pain in many near-by or distant regions. Some attempted to differentiate “myalgia” from “fibrositis.” Thus Williams and Elkins^{1928, 1929} discussed “myalgia of the head” and “myalgia of the pharynx” (severe sore throat, painful swallowing, occasional hoarseness but negative examination) as functional disorders in muscles sensitized to some chemical agent, perhaps histamine.^{1927, 1928, 1929} Others^{673, 1950} seemed to use myalgia and fibrositis interchangeably. Because the distinctions, if any, are not clear we will discuss both topics under the next section on “Fibrositis.”

FIBROSITIS

This is the most common form of acute and chronic rheumatism (Slocumb^{1624, 1627}), but the term is “too loosely applied and ill-defined” (Ellman and associates⁵²⁴). Because of its variable manifestations “it marches under false banners, assumes numerous disguises, and is known by a variety of aliases” (Swett¹⁷⁶⁰).

Incidence. Fibrositis affected 52 per cent of rheumatic out-patients and 20 per cent of rheumatic in-patients at a British army hospital in one year (Savage¹⁵⁴¹). In another British army series of rheumatic patients 69 per cent had fibrositis (Hutchinson). Among rheumatic American soldiers the relative incidence of fibrositis was only 4.7 per cent of 214 consecutive cases at one army hospital (Boland and Corr). The incidence of nodules was noted by Copeman and Pugh: among 500 soldiers non-tender nodules were found with equal frequency in fibrositic and nonfibrositic subjects, but tender nodules were 10 times more common in those with true fibrositis. In 31 per cent of 100 cases of chronic sciatica in young people fibrositis was the supposed cause

(Jackson). The highest incidence of "rheumatism" occurs in miners; fibrositis affected 42 per cent of 113 rheumatic British miners (Schmidt¹⁵⁵³). It is uncommon in youth, reaching its peak incidence in the fifth decade of life (Steinberg¹⁷⁰³).

Etiology. Two forms of fibrositis, (1) primary fibrositis, (2) a secondary form, from trauma, infection or arthritis, were again described.^{1037, 1624, 1627, 1703} Trauma was considered a common factor,^{674, 1267, 1541} either as a single event or from repeated strain, such as produces lumbago in gardeners or Dupuytren's contractures in racing drivers or surgeons.¹⁷⁰⁰ Foci of infection were considered a minor factor.^{358, 524, 890, 1541} A relation to exposure seemed more definite: half of 50 fibrositic patients were in occupations favorable to the development of rheumatism.⁵²⁴ In miners cold and damp are primarily responsible.¹⁵⁵³ Copeman^{377, 378} suggested that such factors as chills, damp, trauma may be of secondary importance and will provoke an attack only in the presence of latent "myalgic spots" previously formed during an illness such as influenza. A relationship to influenza was reported in eight of Jackson's cases.

Often the onset or recurrence of "fibrositis" is precipitated by emotional upsets and is alleviated when the life situation improves, according to Halliday.⁷⁴⁷ This view was challenged by Kelly^{978, 979}: "the symptoms can be explained on the basis of known somatic reactions rather than of mystic symbolism or emotional delusion." Others discussed the psychogenic factor.^{524, 682, 890, 1627} Unilateral fibrositis of shoulder muscles in a group of London women was prosaically called "queue-itis" and was presumably due to long holding of market bags (Cutner). Other causal factors mentioned were metabolic and endocrine disturbances,⁵²⁴ postural defects,⁴⁷⁶ coronary heart disease,^{780, 1820} circulatory insufficiency,¹⁷⁰⁰ plumbism and alcoholism.¹⁷⁰³ Steinberg¹⁷⁰³ considered primary fibrositis a metabolic disorder related to vitamin E deficiency.

Clinical Data. Fibrositis was defined as an acute, subacute or chronic condition affecting subcutaneous tissues, fibrous origins, insertions and aponeuroses of muscles, fibrous portions of joint capsules, fascial ligaments or tendons and supporting tissues of certain nerves (Collins³⁵⁸). Physical examination may be negative.⁵²⁴ Many authors recalled the idea of Kellgren (1938)¹¹ that the muscular pain may be referred, the site of local tenderness being quite apart from the site of the pain. Common sites for fibrositic lesions were described.^{673, 677, 890, 978, 1037, 1631, 1703, 1825, 1950} Fibrositis is a common cause of low back pain,^{862, 973, 1541} sciatica,^{245, 760, 862, 904, 972, 1541, 1720} or postoccipital pain and headache.^{972, 975, 1267, 1376, 1541, 1730, 1928} It must be considered in the differential diagnosis of shoulder pain.^{111, 978, 1541, 1829} Fibrositic lesions of chest wall and around knee and foot were described.^{972, 977, 979, 1631}

[Feet are rarely, if ever, affected by *primary* fibrositis.—Ed.]

The rôle of fibrositis of abdominal, dorsolumbar or psoas muscles in the production of abdominal pain which may easily be confused with visceral lesions was stressed by many.^{720, 760, 789, 862, 973, 1267, 1622, 1760, 1825} In 50 cases low abdominal pain was attributed to psoas fibrositis (Greene). Fibrositis may produce thoracic pain^{973, 1760} which sometimes resembles angina.^{215, 862, 1267} The "dorsolumbar syndrome" was vaguely defined as a localized fibrositis of the back with pain referred along the twelfth thoracic and first lumbar nerve producing symptoms in back, abdomen, groin or scrotum.¹⁶²² Fibrositis of orbital muscles was reportedly encountered.⁴⁷¹

In diagnosis, Mester's "specific reaction" was not found of value (Copeman and Stewart). Diagnostic movements to localize deep-seated lesions were outlined (Cyriax ⁴²⁰).

[Obviously old confusions still prevail. Since the manifestations of primary fibrositis are largely, if not entirely, subjective, many "aches and pains" of diverse nature and cause are erroneously labeled "fibrositic." Studies on the relative frequency of rheumatic diseases among British troops indicate an incidence of "fibrositis" many times that among American troops subject to the same etiologic factors, and that no cases of "psychogenic rheumatism" were listed as such. We suspect that many of these cases of "fibrositis" among British soldiers and civilians ⁵²⁴ really were of "psychogenic rheumatism."

We are skeptical about "abdominal fibrositis." In our experience many vague abdominal pains, the cause of which physicians cannot determine, are "disposed of" as "fibrositis of abdominal muscles." If this is so, why do not the "fibrositic abdominal muscles" react to rest, changes in weather, sleep, exercise, heat, cold, as do fibrositic muscles elsewhere? The whole subject of primary fibrositis needs more critical appraisal and much more study. It is regrettable that we know so little about disease of skeletal muscle which comprises 40 per cent of the weight of the human body and is even more available for biopsy than articular tissues.—Ed.]

Pathology and Laboratory Data. Older ideas on pathology were reviewed.^{243, 358, 682, 1730} But recent studies did not reveal any characteristic tissue change.^{358, 608} Steinberg ¹⁷⁰³ considered the pathologic changes of primary fibrositis similar to those of nutritional muscular dystrophy.

Creatinuria was found in 19 of 20 patients with myosis (myalgia), the output being somewhat proportional to symptoms.²¹⁵ Electromyographic examination of fibrositic patients has shown increased localized irritability of muscle in some cases (Elliott ^{518, 519}), but no abnormality in most (Brøckner-Mortensen and Clemmesen ²¹⁵; Buchthal and Clemmesen). No change in liver function or plasma volume was found (Robinson ¹⁴⁸⁰). Blood studies were of little help; sedimentation rates were usually normal,^{727, 1624, 1627} but may be elevated (Race; Swett ¹⁷⁶⁰). An elevation of blood uric acid in some cases suggested a gouty basis (Buckley ²⁴³; Race). The plasma fibrinogen level was increased in "chronic muscular rheumatism" (Mester ¹²²⁴). The urinary excretion of vitamin C was usually decreased, that of indole increased (Race).

Treatment. The value of rest, heat, massage, salicylates and correction of postural defects were again noted. Rest is essential in acute cases.^{470, 890, 1760} Skilled, heavy massage^{471, 789, 1037} and "stretching" exercises¹⁰³⁷ were recommended. Such measures are effective even in "the fibrositis of old age."⁸⁷⁴ Most writers reported successful results from the injection of local anesthetics into "trigger points,"^{424, 673, 677, 972, 975, 977, 1541, 1622, 1829} but Hutchison ⁸⁹⁰ stated that his early enthusiasm for such injections had been tempered by further experience. Failures resulted when all tender areas were not clearly identified and infiltrated.^{1267, 1825, 1950} Equally good results were reported from injections of isotonic glucose solution (Ray ¹⁴³⁹). Elliott ^{518, 519} warned against the diagnostic use of infiltration: myalgia may arise in muscles supplied by an irritated root, which simulates fibrositis; therefore, relief from procaine does not exclude a root lesion. Dehydration gave relief in 13 and failed in nine of 22 patients with typical fibrositis (Copeman and Pugh). Intramuscular injections of neostigmine gave rapid relief in nine acute cases of cervical fibrositis and marked improvement in one of six years' duration (Kabat and Jones). [These nine acute cases were of "acute torticollis" or "stiff neck," which is almost always a short, self-limiting disease. Since many such cases are relieved spontaneously within a few days or even hours the results cannot be ascribed definitely to neostigmine.—Ed.] Some

tender spots responded well to freezings with ethyl chloride.⁷²⁰ Of nine patients treated with bee venom, one was cured and eight "markedly improved."⁶⁹ Bogomoletz' "A.C.B. serum" was not helpful (Bach⁴⁸). A stock streptococci-staphylococci vaccine was used by Crowe⁴¹⁰ on 89 children with "nonarticular rheumatism." "Profound changes in their well-being" presumably occurred.

Steinberg^{1703, 1705} contended that vitamin E is necessary for the prevention and cure of the particular type of connective tissue change in primary fibrositis, the pathology being strikingly similar to that of nutritional muscular dystrophy in young rats; 143 of 145 cases were successfully treated by the oral or parenteral administration of tocopherol. It had no value in secondary fibrositis.^{1700, 1702} Ant concluded that the direct application to the fibrositic site of vitamin E by inunction was beneficial, "apparently exerting a relaxant effect on muscle fibers, relieving tenseness and tautness and acting as a 'lubricant' to prevent tissue injury through hydremia." [The only case reported was one of frost-bite.—Ed.] But others considered the value of vitamin E for myopathies to be "purely speculative" (Mims¹²⁴⁷) or psychotherapeutic (Milhorat¹²³⁸). [The value of vitamin E in fibrositis or the myopathies remains uncertain.—Ed.] Deep roentgen therapy was considered useful in traumatic fibrositis.¹⁷⁶⁰

An illustration of prevention was reported by Schmidt¹⁵⁵³ who studied the incidence of rheumatism in three coal mines and found no fibrositis (excluding lumbago) in one which had pit-head baths. [The statistical data given were too limited to permit an independent conclusion.—Ed.]

MISCELLANEOUS DISEASES OF MUSCLES AND FIBROUS TISSUE

Nocturnal Muscle Cramps. Night cramps in calf muscles occur with many conditions but especially with chronic (rheumatoid or osteo-) arthritis which was present in 40 per cent of Gootnick's 30 cases. Concentrations of calcium and phosphorus in blood were normal. The cramps, previously unrelieved by the use of calcium salts or aspirin, were promptly relieved in 90 per cent of cases by one daily (bedtime) dose of quinine sulfate (usually 3 grains; 0.2 gm.). The rationale was discussed.

Dermatomyositis; Polymyositis. Several cases were reported,^{592, 668, 900, 1056, 1617} including two in Negroes in which detailed studies of skin were made (Irgang⁸⁹⁸). Hecht⁸⁰⁴ reported five cases in children, with two deaths; four of these were complicated by calcinosis universalis. A case of "acute benign dermatomyositis" with recovery was noted (Leys¹⁰⁰⁶). Among other manifestations described were mild fever, muscle tenderness, arthritic pains without localized swelling of joints, vasomotor phenomena and creatinuria.^{504, 909, 1617} The similarity and relationship of dermatomyositis to other conditions with diffuse involvement of collagen (the "dermatoscleroses") were again considered but no new conclusions were presented.^{71, 898, 1216} The lesions in skin and their differentiation from lupus erythematosus were discussed (Keil).

Localized or generalized involvement of skeletal muscles with nonsuppurative inflammation and degeneration of many fibers were constant findings. But these changes were not regarded as specific for the disease because of histologic variation.⁹⁰² Proliferation of sarcolemma nuclei and peripheral vascular changes were not uncommon.¹⁶¹⁷ Indistinguishable lesions were found in acute rheumatic

fever, lupus erythematosus and myotonia dystrophica.⁹⁰⁹ Jager and Grossman⁹⁰⁹ considered the changes in muscle not unlike those seen by Curtis and Pollard (1940)^{1h} in rheumatoid arthritis.

No new therapeutic measures were described. Creatinuria was reduced by the administration of fresh, vacuum-packed wheat germ, also by soy bean lecithin, but no effect on the dermatomyositis was claimed.¹²³⁹

Scleroderma. Generalized scleroderma constitutes one of a group of diffuse collagenous diseases of unknown etiology, which includes dermatomyositis, disseminated lupus erythematosus, acrosclerosis (Klemperer, Pollack and Baehr¹⁰¹⁶). "Striking similarities in the detailed pathology of these various conditions require evaluation for a possible relation or common denominator" (Banks⁷¹). To replace "scleroderma" the term "progressive systemic sclerosis" was proposed, as scleroderma is only part of a systemic disease, the most serious lesions of which actually occur in viscera (Goetz⁶⁶⁰).

In extremities stiffness in joints and muscles, tendon contractures, osteoporosis and arthropathy with absorption of the bones of digits develop.^{136, 1008} Deposition of calcium salts is likely in subcutaneous tissues, particularly in regions subject to pressure.^{274, 660, 903, 944, 1786, 1908} Generalized scleroderma and acrosclerosis were distinguished sharply; the latter was related more closely to Raynaud's disease (O'Leary¹³¹⁶ and Waisman).

Described were the pathologic lesions in skeletal muscles,^{136, 1908} arterioles, collagen tissue,^{136, 1278, 1307} lungs, heart, esophagus, gastrointestinal tract and kidneys.^{136, 660, 737, 903, 1278, 1397, 1419, 1908}

There is no specific treatment.⁴⁹¹

Calcinosis. Calcinosis occurs alone^{1136, 1356} or in association with scleroderma,^{127, 274, 660, 903, 944, 1786, 1908} acrosclerosis¹³¹⁷ and dermatomyositis.^{80, 804} Differentiation of the two types, namely, calcinosis circumscripta and calcinosis universalis, is applicable only to characteristic examples; individual cases are frequently indeterminate.¹⁷⁸⁶ Serum calcium and inorganic phosphorus were normal.^{80, 274, 944, 1308, 1356, 1786} Consistently elevated blood uric acid was reported in one case.¹³⁵⁶ Abnormal calcification in muscles of forearm, as found in devitalized tissue, was discussed.¹⁵⁸⁵

Treatment has been unsatisfactory. No improvement from sympathectomy was observed (Nuñez and Arthur¹³⁰⁸). Unilateral parathyroidectomy was of little value in one case (Byron and Michalover²⁷⁴), beneficial in another in which many calcific deposits disappeared (Bartels and Catell⁸⁰).

Arthrogryposis Multiplex Congenita. This embryonic malformation is best explained by arrest of normal embryonic development. The term means a crooked joint. However, the contractures of joints are secondary, the initial lesion being a primary aplasia or hypoplasia of certain muscle groups. Other terms used have been "amyo-plasia congenita" or "myodystrophia foetalis deformans," to indicate that the deformities result from fatty degeneration of muscles during intrauterine life. Features include articular rigidity, congenital defects (club foot or hand, dislocated hips), abnormal posture, poorly developed muscles. Eighteen children described had "a stuffed sausage-like appearance," little palpable muscle, periarticular thickening and contractures (Katzeff). Histologically atrophy and fat replacement of involved muscles occur. Treatment included manipulations with or without anesthesia, supports, surgical corrections; definite improvement resulted (Katzeff; Badgeley⁵¹).

MISCELLANEOUS CONDITIONS

Herniations of Subfascial Fat. These were found by Copeman and Ackerman to be the cause of certain cases of "backache" or of supposed "fibrositis" of muscles of back. In characteristic regions, especially about the lumbar, gluteal or episacroiliac regions of soldiers with supposed "fibrositis," painful trigger points or myalgic spots were discovered, sometimes also tender subcutaneous "rheumatic nodules." To determine their nature the backs of 14 soldiers who died of various causes were dissected. A "basic fat pattern" was discovered which coincided with the regions in which "fibrositic pain" and nodules had occurred in life. But instead of finding subcutaneous fibrous nodules Copeman and Ackerman found small herniations of lobulated fat penetrating through fascial tears (weaknesses, deficiencies) or through the unprotected foramina by which the posterior primary rami of the first three lumbar nerves pierce deep fascia. The fat protruding was pedunculated, nonpedunculated or foraminal. Pain was ascribed to edema in the lobules and tension which may lead to herniation if fascial walls are deficient. At necropsy the bubbles of fat, found in the lumbar region, could be converted into tiny hernias by pressure on adjacent tissue. Conversion from bubbles to true hernias during life was attributed to incidents such as sudden trauma, sudden flexing of back or prolonged rest in the supine position.

Tender subcutaneous nodules were removed surgically from 20 patients with localized or disseminated back pain and proved to be herniated fat with no evidence of inflammation; hence such hernias were believed the cause of "trigger zones" in certain cases of supposed fibrositis. In later cases Copeman and Ackerman used more conservative treatment. Overlying skin was anesthetized, the nodule was transfixated with a cutting needle from which 10 to 20 c.c. procaine solution was injected; the needle was then swept around to undercut the nodule and thereby to disperse edema and tension. The pain and tenderness of the pre-existing "fibrositis" were often thus relieved.

Further anatomic and clinicopathologic studies were made by Mylechreest who successfully treated four patients by surgical removal of herniated fat and also by Herz who similarly relieved six patients with severe subacute or chronic backache.

[In the past certain physicians, including some of us, have often felt low on the back, especially in the sacroiliac region, tender or nontender nodules of different sizes which were suspected of being subcutaneous fibrositic nodules, clinically active or inactive. But when certain nodules were removed only fatty tissue was present and their nature was not understood even though some patients were curiously relieved of symptoms. Thus in 1935 Sntro found such nodules in sacroiliac regions in 55 per cent of 170 unselected hospital patients, a third of whom had low back pain. He removed some nodules but found only noninflamed fat and considered them "protective buffer pads" unrelated to symptoms despite the relief in some cases. In 1937 Ries found "episacroiliac lipomas" in 317 (32 per cent) of 1,000 patients examined therefore: in 18 per cent of 250 males, in 36 per cent of 750 females. Of the 317 patients with tumors 150 had backache, 167 did not; 231 had bilateral, 86 unilateral tumors. The tumors were "spontaneously painful" in 131, painless in 186 cases. Of the 1,000 persons 309 had lumbosacral backache: 150 with, 159 without tumors. The backache was near the sacroiliac joint with slight radiation. "Some 20 patients" with sensitive

tumors and backache were treated by excision of, or injections of procaine into, the tumors with permanent relief in some, only temporary relief in others. The excised tumors were of encapsulated fat. The pathogenesis was not determined. More recently Buckley wrote²⁴³: "Quite frequently small masses of fat are regarded as fibrositic nodules" and Collins³⁵⁸ found three "typical fibrositic nodules" on removal to be "noninflamed lobulated fat with fibrous encapsulation," "simple lipomata."

The nature of at least some of these subcutaneous "nodules" now is more clear. Recently Copeman and Ackerman (1947) and Herz (1946)⁸³⁷ reported further results from conservative or surgical treatment. The earlier papers of Copeman and Ackerman and of Mylechreest were entitled "Fibrositis of the back" even though the fatty tumors were not fibrous and were obviously not the orthodox "fibrositic nodules" and though the symptoms were proved not to be due to fibrositis. This unfortunate error in terminology was corrected in recent papers. Although we believe these are important reports we must remark again that many such nodules are essentially painless, and some tender ones may not be the cause of the patient's symptoms. We hope that these "new" fat herniations will be handled temperately and not removed uselessly and overenthusiastically. It is premature to conclude now that all tender subcutaneous nodules are fatty herniations or that such fatty (not fibrous) nodules explain most "fibrositis." But these studies constitute an important new approach to the vexing problem of backache.—Ed.]

Psychoneurotic Musculoskeletal Symptoms; "Psychogenic Rheumatism."

1. *Definition.* "Psychogenic rheumatism" must not be confused with organic rheumatic disease (rheumatoid arthritis, rheumatic fever, gout) influenced by predisposing, precipitating or aggravating neurogenic or psychogenic factors. Some physicians state that (1) certain persons inherit a "personality type" which makes them susceptible (inherited susceptibility) to the development of organic rheumatic disease^{487, 744, 745, 747, 1346}; or (2) a normal person may run into chronic emotional stress sufficient to alter his neuroendocrine system, "lower his vitality" and make him susceptible (acquired susceptibility) to organic rheumatic disease; in some such people a serious emotional crisis may appear to precipitate the onset of rheumatoid arthritis¹³⁴⁶; or (3) in a given case the course of an organic rheumatic disease, such as rheumatoid arthritis, is influenced for better or worse by the occurrence or disappearance of emotional stresses.^{744, 1346, 1467, 1751} These circumstances suggest a neurogenic or psychogenic origin of organic rheumatic disease but the resultant disease is *not* psychogenic rheumatism.

Psychogenic rheumatism consists of musculoskeletal symptoms of a purely functional or psychoneurotic type without organic lesions. It is of two forms: primary and secondary. In the primary form (in which no organic rheumatic disease is present) psychic stress is the sole cause of musculoskeletal symptoms which may masquerade as true rheumatic disease; examples are functional "aches and pains" from musculoskeletal tension simulating fibrositis, hysterical contraction of hand or knee simulating rheumatoid arthritis, hysterical flexion of spine (camptocormia) simulating spondylitis. In the secondary form psychic stress produces musculoskeletal symptoms superimposed on a recently healed (functional prolongation) or a currently present and often relatively minor rheumatic disease (functional overlay).

This condition as it appears among civilians has been described vividly by Halliday,^{743, 747} but has been brought to the fore chiefly by recent military experiences excellently summarized by medical officers.^{173, 174, 524, 571, 581, 802, 890, 1544}

2. *Terminology.* No entirely satisfactory name has been coined. It is, of course, "psychoneurosis manifested by musculoskeletal symptoms," but for daily use a less cumbersome, shorter term is required. Various terms have been used: "psychogenic rheumatism,"^{173, 174} "psychoneurotic or psychosomatic rheumatism,"^{743, 1627} "psychoneuroendocrine disorder with fibrositis as a dominant physical symptom,"⁷¹³ "psychogenic fibrositis,"⁹⁷⁸ "arthralgia,"⁸⁰² "neurotic or hysterical joints," "functional or psychogenic muscular disability,"^{1467, 1514} "hysterical 'fibrositic' complaint,"⁵²⁴ "psychogenic back pain,"¹⁵³⁸ "psychalgia."¹⁹⁷⁵ Flind and Barber⁵⁷¹ preferred the psychiatric term applicable to each case: "hysteria (or anxiety or depression) with so-called rheumatic pains." Each term has objectionable features; until a better one appears, "psychogenic rheumatism" will serve if physicians understand that it connotes no *organic* rheumatic disease produced by psychic factors.

3. *Incidence.* Psychogenic rheumatism affected a third of insured patients with "chronic nonarthritic rheumatism" studied by Halliday,⁷⁴³ 35 per cent of 120 "rheumatic patients" at a Royal Air Force rheumatism center (Flind and Barber⁵⁷¹), half of 50 patients with supposed "fibrositis" (Ellman and colleagues⁵²⁴), all of 26 Canadian soldiers with "arthralgia" (Heaton⁸⁰²). It affected a third of 450 American soldiers who had "arthritis or allied conditions" studied by Boland and Corr¹⁷⁴ at an army general hospital, being the commonest cause of disability.^{173, 174} At another American army general hospital 50 per cent of patients admitted for organic neurologic disease really had "functional muscular disability" (Saxe¹⁵⁴⁴).

4. *Clinical Data.* In a minor percentage of cases it took the form of hysterical contractures of extremities with bizarre postures, gaits or limps^{173, 174, 571, 802, 1130, 1538} or contractures of spine (camptocornia).^{748, 1531, 1005} Of 100 psychiatric soldiers 15 per cent complained of "backache."¹¹¹ The great majority of such cases were cases of arthralgia or myalgia or both, usually misdiagnosed as "arthritis," "fibrositis" or "backache."⁵⁸¹ Of 269 psychoneurotic patients studied by Friess and Nelson⁶¹⁵ 57 (21 per cent) complained chiefly of musculoskeletal symptoms ("pains" in muscles more often than joints). All had previously received an erroneous diagnosis and treatment of "arthritis." After a five-year follow-up, there was still no objective or laboratory evidence of organic disease. Chronic fatigue is now recognized as one of the chief symptoms of nervous exhaustion and maladaptation (Kepler). Thus the symptoms of "psychogenic rheumatism" were chiefly of the "skeletal muscle pattern; simple derivatives" were fatigue, weakness, stiffness, drawing sensation, aching (Garner). From the psychiatric standpoint most of the reactions in one group were classified as of the hysterical form with the "resentful" type more common than the "histrionic" or "ailing" type.⁵²⁴ But of Flind and Barber's 42 cases⁵⁷¹ reactions were of anxiety type in 52 per cent, hysterical in 41 and depressive in 7 per cent. Halliday^{743, 717} and Fox⁵⁸¹ interpreted the symptoms largely in terms of symbolism. Thus lumbago or "backache" symbolized resentment, resistance, threats to pride. When rigid, stiff or touchy people become ill, "the rigidity, stiffness and wincing responses of rheumatism" develop. Left-sided pain relates to "sinister" feelings of loss; pains in extremities "may symbolize repressed desires to attack"; "left shoulder neuritis" so often is "a neuritis of deprivation, not of vitamins but of a married partner or other dearly beloved person or object." But Abrahams hesitated to accept such a symbolic interpretation of "fibrositis." Regardless of their pathogenesis or meaning the pains are more real than generally believed; as Kelly stated⁹⁷⁸: "Psychogenic pain

should not be divorced from reality, for all pains are peripherally induced and subjectively appreciated."

5. *Etiology.* Among soldiers the precipitating factors included the conflicts, frustrations and dangers incident to military service (Boland and Corr), but most of them had demonstrated psychoneurotic reactions from childhood (Flind and Barber⁵⁷¹; Heaton⁸⁰²). Thus the remote factor of unstable personality plus the immediate precipitating factor of an (to them) intolerable situation combined to produce symptoms which largely represented an escape mechanism, a flight into illness. Boland and Corr observed that a history of rheumatic disease sometimes provided a suggestion which the psychoneurotic unconsciously adopted to suit his purposes. The emotionally unstable person will elevate a minor intermittent (rheumatic) discomfort to the status of a major disability.⁸⁰² One of Heaton's⁸⁰² patients used a genuine (but minor) disability of knee "for more than it was worth" for a year; then when rebuked for this he had multiple pains without discoverable organic basis. Thus a harmless crepitation of knee or a knuckly finger may be offered by the psychoneurotic as bona fide evidence of organic rheumatism to explain widespread functional complaints.⁵⁷¹

6. *Diagnosis.* Methods of diagnosis were carefully described and included the type of past history usually found, previous attacks of conversion hysteria of non-rheumatic type, personality appraisal, physical examination including study of face and manner,^{746, 1407} absence of significant evidence for organic disease.^{174, 571, 743, 740, 747, 1130, 1544} Muscle analyses demonstrated hysterical overreactions, overdramatization of affected parts, writhing, groaning, lack of consistency of painful motions.^{571, 1130, 1544} Electrical testing gave useful confirmation.¹⁵⁴⁴ An abridged psychiatric examination suitable for practitioners was described.^{524, 571, 743, 716} Narcosynthesis involving intravenous injections of pentothal or amytal proved most useful.¹⁵⁴⁴ The differentiation of psychogenic rheumatism from "true fibrositis"^{571, 743, 747, 802, 1627} and from malingering^{174, 571} was described. "Iatrogenic (physician-induced) rheumatism" might be defined as the psychogenic rheumatism mistakenly called "organic rheumatic disease" by an unwary physician. "'Fibrositis' is apt to be the physician's escape from reality" (Heaton⁸⁰²). A mistaken diagnosis is serious as it represents an "authoritative affirmation to the patient of a nonexistent condition" (Saxe¹⁵⁴⁴).

7. *Treatment.* These included "explanation, persuasion and re-education."⁵⁷¹ Symptoms often disappeared during or after narcotherapy.¹⁵⁴⁴ Physical therapy was of little or no value⁸⁰² and the pains should not be treated per se because "they merit no more special attention than the tachycardia of an anxiety state" (Flind and Barber⁵⁷¹). Camptocormia among soldiers was sometimes successfully treated by narcotherapy or the "tilt-table treatment,"¹⁹⁰⁵ by postural training,⁷⁴⁸ less often by suggestion. But in some cases the only "cure" was discharge from the army.¹⁵³¹ In civilian life psychotherapy is often successful but, despite explanation and persuasion, symptoms often continue until the irritating situation is improved (Halliday). Despite psychotherapy most of the patients of Friess and Nelson⁶¹⁵ after a lapse of five years had the same complaints as before. "This fixity of the complaint is but one manifestation of the basic changelessness of the psychoneurotic patient and probably represents his most outstanding characteristic." In the treatment of chronic fatigue

and nervous exhaustion the proper ratio of work, worship, play and love is of profound importance (Kepler). Because psychogenic rheumatism is not a precursor or "forme fruste" of organic rheumatism these patients are not especially liable to develop arthritis later despite their severe and persistent psychogenic rheumatism.⁸⁰²

The Shoulder-Hand Syndrome. This was discussed under "The Painful Shoulder."

Disseminated Lupus Erythematosus. Unusual interest in this disease was reflected by the publication of 52 reports with many general discussions during the period of this review.^{64, 94, 178, 318, 483, 624, 625, 821, 981, 1114, 1163, 1166, 1167, 1168, 1178, 1209, 1431, 1581, 1635} The name, "subacute nonrheumatic arthrosclerosis," was proposed (Proger). Etiology still remains a mystery. Considerable support was expressed for its allergic nature.^{281, 383, 1398, 1731} The antigens suggested were sulfonamide-protein, actinic rays, transfused blood and horse serum; Fox⁵⁸³ wondered if this malady might be in the nature of chronic serum sickness.

The vascular and perivascular lesions which characterize this disease were described.^{71, 910, 1116, 1579} These arteriolar changes are the common denominator of lupus erythematosus, scleroderma, dermatomyositis, Libman-Sacks syndrome and periarteritis nodosa. In earlier papers Klemperer, Pollack and Baehr^{1016, 1017, 1018} considered lupus erythematosus primarily a vascular disease, but recently they emphasized that the fundamental pathology is a widespread damage to the collagenous tissues of which the vessels are only a part. The characteristic organic changes are local manifestations of widespread fibrinoid degeneration of collagen, a biophysical change which results in derangement of this extensive colloid system ("organ"). Patchy pulmonary inflammatory infiltrations,¹⁴²⁹ hyperglobulinemia^{335, 1776} and false positive Wassermann reactions were noted.¹³⁰¹ Keil compared the lesions of skin and mucous membrane with those of dermatomyositis. Lesions of the central nervous system and resulting symptoms were described.¹²⁵

Of note was the common occurrence of arthralgia or of acute or chronic arthritis. Articular pain and stiffness, sometimes swelling and limited motion were prominent at times during the illness in most of the new cases reported. Often the articular symptoms constituted the chief complaint; many times they appeared weeks or months before the skin lesion.^{64, 71, 287, 318, 327, 355, 425, 483, 583, 714, 863, 908, 1016, 1163, 1166, 1168, 1179, 1354, 1391, 1416, 1429, 1134, 1416, 1579}

"Migratory evanescent arthritis" occurred in 23 (77 per cent) of 30 cases.³⁵⁵ Articular symptoms may last six months to six and one-half years.⁷¹⁴ In some cases the articular involvement resembled rheumatoid arthritis¹¹⁶⁸; indeed such a diagnosis was sometimes erroneously made.⁹⁰⁸ Permanent articular changes are rare¹¹⁶⁸ but deformities, involving small joints and usually appearing late, have been reported.³²⁷

The "rheumatic symptoms" of disseminated lupus were contrasted with those of periarteritis nodosa; in the former, symptoms are generally articular, less often muscular,^{287, 318, 483} whereas in periarteritis nodosa the pains are more likely to be muscular or neuritic than articular since polymyositis and polyneuritis of peripheral type are common.^{71, 1163}

Pathologic studies of affected joints have been meager.³²⁷ In one case "marked synovitis but no evidence of rheumatoid arthritis" was noted.¹¹⁶⁷ In two of six other cases "synovial joint changes" were found but not described (Guion and Adams). In another case of swollen painful joints no articular

pathology was found at necropsy (Bauer and MacMahon). Hypertrophy of synovial villi, inflammation with perivascular infiltration in subsynovial and capsular tissues, formation of subperiosteal bone and hyperplasia of synovium have been previously reported (Cluxton and Krause).

[It is regrettable that joints were so rarely examined at necropsy even in those cases in which articular symptoms were dominant early features. From 60¹¹ to 77 per cent³³⁵ of these patients have symptoms which may resemble periarticular or intramuscular fibrositis, subacute or chronic rheumatoid arthritis or even acute rheumatic fever. Recent studies in fatal cases gave minute details of practically all bodily tissues including brain, bone marrow, even tongue and eyes, but not joints. Apparently the synovial cavity is the "last frontier" for most pathologists. Let us encourage appropriate necropsy studies in fatal cases in which articular symptoms are notable.—Ed.]

Treatment remained a problem. Articular lesions generally do not respond well to treatment.^{327, 1579} Cures of the disease with sulfonamides were reported,^{863, 1354} but some physicians¹³⁹⁸ cautioned that sulfonamides might produce untoward effects. Liver extract was considered helpful^{388, 1003}; treatment with iodine²⁸⁷ and removal of "foci" of infection were advised.^{1677, 1792} Sosman stated that "spray roentgen-ray therapy has given very promising results." A seven-year recovery from acute disseminated lupus erythematosus without special treatment was reported in a male child (Horstmann). Aurotherapy was still considered "the most efficacious remedy" by Bechet.

Periarteritis Nodosa. For this disease some physicians preferred the terms, "primary arteritis"⁹⁶⁴ or "polyarteritis."^{1143, 1696}

1. *Etiology.* This has been attributed to virus, different bacterial agents, toxins and disease of central nervous system, but the likelihood that it is due to hypersensitivity was strongly suggested by Rich^{1456, 1457, 1458, 1459, 1460} who noted the development of periarteritis nodosa in patients shortly after they had serum sickness, hypersensitive reactions to sulfonamides or iodine. Apparently substances of widely different chemical nature may cause this destructive vascular disease by their ability to induce anaphylactic hypersensitivity. Rich¹⁴⁶⁰ produced, experimentally in rabbits, typical diffuse periarteritis nodosa by a condition analogous to human serum sickness. Development during thiourea therapy was reported in one case (Gibson and Quinlan) and thiouracil produced "periarteritis nodosa-like" lesions in rats (Marine and Baumann). But McCall and Pennock¹¹⁸³ could not correlate the disease in 10 cases with previous sulfonamide therapy. By giving large overdoses of desoxycorticosterone acetate Selye and Penz produced vascular lesions in rats similar to those of periarteritis nodosa, malignant hypertension and rheumatic fever. Lesions of periarteritis nodosa also were noted in two cases regarded clinically as cases of trichinosis, with trichinellae in muscles. Trichinosis, with its strong allergic manifestations, also may be a cause of this arterial disease (Reimann, Price and Herbut¹⁴⁴⁹). In another case periarteritis nodosa and encysted trichinellae were found at death (Banowitch, Polayes and Charet).

2. *Clinical Data.* Numerous studies appeared.^{58, 196, 273, 558, 959, 1089, 1100, 1105, 1133, 1171, 1242, 1274, 1571, 1609, 1696, 1720, 1789, 1876, 1957} The disease affects four males to one female.¹⁵⁷⁹ Cases in children^{337, 1562} and in an infant one month old were noted.¹⁹³⁴ Clinical features were reviewed: variable fever and leukocytosis with a wide variety of symptoms depending on which, or how much each, system is affected by the diffuse arteritis, the usual order of frequency being lesions in

kidney, heart, gastrointestinal tract, mesentery, liver, muscles, nerves.^{550, 1184, 1579, 1677} Common in some cases were fever, leukocytosis, eosinophilia and asthma¹⁴⁹; in others fever, nephritis or intestinal symptoms, polyneuritis and polymyositis.⁷³ A notable eosinophilia occurs in 10 to 14 per cent of cases.

Muscles are affected clinically and pathologically in 30 to 35 per cent,^{1579, 1677} joints less frequently. In recent cases early symptoms were muscular aching and tenderness either localized (in calf, leg, neck) or widespread,⁷³ muscle pain of varying intensity (at times sufficient to prevent standing or use of an extremity),^{73, 667} muscle spasm,⁵⁵⁰ cramps, atrophy,^{73, 558} sensory changes in extremities (weakness, numbness, tingling, "pins and needles"),^{73, 550} painful clumsy motion (dysarthria).¹¹⁴⁷ All these result from polymyositis and polyneuritis. Myalgia affected 64 per cent of Jones's cases,⁹¹⁹ all of McCall and Pennock's.¹¹⁸⁴

Articular symptoms of other patients were "painful feet,"¹⁵⁶² pain in wrist without redness or swelling,⁷³ painful shoulders,¹⁴¹ painful swollen ankles,¹³⁵³ weakness and wasting of hands,⁵⁵⁰ painful knees, wrists and elbows.⁶⁶⁷ One case in which febrile polymyalgia with swollen ankles and arthralgias elsewhere were present resembled a case of "rheumatic fever."⁵⁵⁸ "Arthritis (pain and/or swelling)" occurred in 57 per cent of Jones's 14 cases.⁹¹⁹ Pains in muscles or joints affected all of 12 adult patients,¹¹⁸⁴ 50 per cent of 44 children.⁹⁶⁴ Tenderness, weakness and soft pitting edema of legs affected three patients.¹¹⁴³

Pathologic studies of muscles at biopsy or necropsy showed minute foci of "chronic interstitial myositis,"⁵⁵⁸ "angiomiositis,"⁹¹⁹ healed panarteritis in pectoral muscle or mild periarteritis of orbital muscle,⁷³ periarteritis and patchy degeneration of adjacent muscle fibers.¹¹⁴⁷ Biopsy of muscle was "positive" for periarteritis nodosa in five of Jones's nine cases but it often shows only "nonspecific focal myositis."⁵⁵⁸ Joints, bursae and tendon sheaths may reveal granulomatous, not just vascular, lesions.⁹⁵⁹ Bauer¹¹⁶⁶ reported on one patient with "marked synovitis"; typical vascular lesions of periarteritis nodosa affected synovial blood vessels.

Special features (unrelated to muscles or joints) were discussed.^{141, 195, 825, 1143, 1147, 1562, 1889, 1895} In one case the vascular process was healed,¹⁴⁹ but the "healing" results in a progressive, irreversible ischemic process which causes death, generally by renal damage.¹¹⁸³

Diagnostic aids included biopsies of muscle or periarteritic nodule, the presence of a "unique urine" (erythrocytes, red cell casts, oval fat bodies, fatty and broad casts, excess protein)¹⁰³⁵ and sigmoidoscopic detection of characteristic intestinal lesions.⁵⁵⁰ Periarteritis should be considered in any chronic illness⁷³ especially with obscure sepsis, vague abdominal symptoms, polymyositis, polyneuritis, wasting, renal insufficiency, hypochromic microcytic anemia and eosinophilia.¹⁸⁰¹ The similarities and differences between periarteritis nodosa and disseminated lupus erythematosus were discussed,^{71, 1163, 1166} also the possible relationships with rheumatic fever.^{558, 919, 939, 964, 1183, 1184}

In certain cases features suggestive of trichinosis were present (muscle pains, eosinophilia, periorbital edema)¹⁵⁷¹; in others periarteritis nodosa and trichinosis co-existed, perhaps causally.¹⁴⁴⁰

3. *Treatment.* This is unsatisfactory; the disease is usually fatal. Most writers considered therapy only supportive. An apparent cure with sulfapyridine was noted⁶⁶⁷ but others considered sulfonamides useless.¹¹⁴⁴ "Spray roentgen-ray therapy may be of some benefit."¹⁶⁷⁷

Sarcoidosis; Benign Lymphogranuloma. Sarcoidosis or benign lymphogranuloma is a generalized disease that may involve any organ in the body; it

thereby produces many clinical syndromes. Granulomatous lesions of skin were called "lupus pernio"; characteristic changes in bone were named "osteitis tuberculosa multiplex cystoides"; ocular lesions, parotitis and facial palsy was called "uveoparotid fever." But these are all parts of one disease; other synonyms are Boeck's sarcoid or Besnier-Boeck-Schaumann syndrome. The history of the disease was reviewed.^{585, 955}

1. *Clinical Data.* Lymph nodes, lungs and bone are most often affected. Bone lesions affect 10 to 20 per cent of cases; those in the 10 cases of Katz, Cake and Reed⁹⁵⁵ were usually in phalanges, metacarpals and metatarsals. Joints per se are not involved but arthralgia may occur.⁹⁵⁵ Circumscribed cysts are the most common osseous lesions but a reticulated appearance with thickened trabeculae and rarefaction of surrounding bone may occur; swelling and deformity, mutilation or even amputation may result.^{769, 955} Sarcoid tissue may produce tenosynovitis, intramuscular nodules and subcutaneous tumors (Frank⁵⁸⁵).

Thirty-two cases were reported.^{484, 585, 769, 955, 1201, 1395, 1516, 1740, 1797} Clinical and postmortem findings in 43 cases were collected from the literature (Rubin and Pinner). There are few constitutional symptoms: sometimes weakness, fatigability, anorexia, loss of weight or arthralgia occur. Symptoms are caused by mechanical interference with the function of organs, not by intoxication. Sarcoid lesions exert pressure on normal tissue and thus displace or destroy it.⁹⁵⁵

Serum calcium is normal or slightly elevated; alkaline phosphatase is increased.¹⁷⁴⁰ Plasma globulin and sedimentation rates may be elevated.

2. *Differentiation.* The osseous features of sarcoidosis must be distinguished from tuberculous dactylitis, osteomyelitis, gout and rheumatoid arthritis. The distinction between "osteitis tuberculosa multiplex cystoides" (sarcoidosis of bone) and multiple cystic tuberculosis of long bones was discussed: in the former the tuberculin reaction and tests on guinea pigs usually are negative; there occur slow healing, honey-combed areas of bone rarefaction without periostitis, fibrosis or sinus formation, rarely involvement of long bones, frequent involvement of skin (lupus pernio) or lungs (Sweet and Abramson).

3. *Etiology.* The idea that this is a benign form of tuberculosis was not generally supported by recent writers. The presence of neutropenia and leukopenia suggested to some⁹⁵⁵ that a virus was responsible but others disagreed.⁴⁸⁴ Although most patients with erythema nodosum have no pulmonary signs or symptoms, Kerley^{985, 986} often found massive enlargement of bronchial glands with or without infiltration of lungs. From a study of 37 such cases he concluded that erythema nodosum with visceral lesions represents sarcoidosis: "It would appear that 'erythema nodosum-sarcoidosis' in Europe and 'erythema nodosum-coccidioidomycosis' in California are, if not the same disease, closely related."

4. *Treatment.* Roentgen therapy to lungs was helpful in most of 14 cases.¹³⁹⁵

Painful Osteoporosis; Causalgia; Nontraumatic and Posttraumatic Osteoporosis (Sudeck's Atrophy). Painful osteoporosis may be posttraumatic or nontraumatic. The former is more common and has followed contusions, sprains, fractures, bites and burns of mild or severe degree. Less common is postoperative painful osteoporosis from the "trauma" of a simple uninfected surgical procedure. In Buchman's case²³⁶ one week after surgical treatment of stenosing tendovaginitis of the thumb a painful stiff hand, wrist and shoulder with swelling, heat, duskiness of hand, painful stiffness of hand and shoulder, spotty rarefaction in roentgenograms of fingers and wrists and to a lesser degree

in elbow and shoulder developed. After 18 months the condition slowly disappeared. In another case, reported by Brown,²²² a foot was affected after a sprain and was relieved three months later by lumbar sympathectomy.

The cause is unknown but involves a vasomotor disturbance which produces hyperemia in bone, increased vascularity, thinning of bone lamellae and filling of the interlamellar spaces with fibrous tissue. Hyperemia in soft tissues produces duskiness, edema, local heat, periarticular thickening and limited motion. The circulatory disturbances are presumably functional in nature, sympathetic in origin. Normally every trauma evokes an immediate vasoconstriction of the injured part which soon gives way to vasodilation. If the latter persists, painful osteoporosis may result. "The paradox is that a sympathectomy which of itself increases vasodilation, usually brings immediate relief": so wrote Buchman.²³⁶

1. *Pathogenesis.* The syndrome somewhat resembles the "shoulder-hand syndrome" already described; the two may be closely related although the former is supposedly related to hyperemia, the latter to ischemia. An explanation of painful osteoporosis was offered by DeTakats in two informative papers^{463, 464} which we will review in some detail because of their importance.

Sudeck's atrophy, Lériche's posttraumatic osteoporosis, Weir Mitchell's causalgia, peripheral trophoneurosis, reflex dystrophy and chronic traumatic edema all result from the same mechanism. Certain nontraumatic irritative lesions in any of the three sensory neurons which are capable of producing chronic spreading hyperalgesia also will invoke this mechanism. The location and anatomic connections between the first, second and third order (sensory) neurons was described. Lesions of the first sensory neuron are produced not only by various types of trauma but also by certain diseases such as periphlebitis or lymphangitis. Apoplexy of cauda equina, poliomyelitis, tabes, syringomyelia and other diseases may produce lesions of the second (higher) sensory neuron. Cerebral thrombosis, infarcted cortex with painful hemiplegia, brachial plexus injuries constitute lesions of the third (highest) sensory neuron. Peripheral trauma activates the first (lowest) neuron producing vasomotor reflexes which under certain conditions are predominantly vasodilator. The trauma which induces causalgia results, not from major injuries to bones, joints, nerves or blood vessels, but usually from minor injury (sprains or minor fractures) to foot, ankle, hand or wrist. Thus the character of the initial trauma allows no prediction as to its late sequelae. The trauma producing Sudeck's atrophy seems to activate both vasoconstrictor and vasodilator fibers with dominance of vasodilators. This produces increased capillary pressure and stimulation of sensory receptors with the resultant throbbing, burning pain of causalgia. Lewis (1936) postulated the secretion of a pain substance at the termination of nerve fibers belonging to the posterior root system. (Since these fibers were neither sensory somatic nor sympathetic fibers, he named them "nocifensor nerves.") It is not clear whether the substance produced at the nerve endings is acetylcholine or histamine; both have been recovered after stimulation of posterior root fibers. In irritative lesions in any of the three sensory neurons a group of fibers is activated which secrete pain-producing, vasodilator substances at nerve endings. In the causalgic state (unlike other painful states which lead to continuous afferent impulses) there is an efferent stimulation of pain-producing vasodilator substances which, unless blocked or neutralized early, will lead to the sensitization of higher and higher levels.

Three stages of the syndrome were mentioned by DeTakats.^{463, 464} Features of the first stage include severe persistent burning pain, paroxysms produced by jarring, air currents or emotional upsets, warm dry extremity, edematous subcutaneous and periarticular spaces, spastic muscles attempting to splint wrist or ankle, increased cir-

ulation to the injured part as shown by blood flow and oscillometric curves. In this stage pain remains limited to injured site; osteoporosis is absent since hyperemia for four to six weeks is necessary for its production. In this stage the process may cease to develop or be combated by adequate treatment.

If not, the second stage appears and includes spreading periarticular edema, less warmth and flushing, cyanosis, cold and hardness of affected part, stiffening of joints, muscular atrophy, spotty osteoporosis, a less active blood flow but with more vasodilation in the affected than in the uninjured limb, a painful spreading neuralgia or hyperalgesia which may defy segmental distribution. In this stage the condition is still amenable to treatment.

In the third and final stage there occur progressive atrophy of skin, muscles and bone with extensive osteoporosis of nonspecific appearance, intractable pain spreading to the root of a limb or even to the trunk.

The feature of osteoporosis has been overstressed; a diagnosis of Sudeck's atrophy cannot be made on roentgenograms alone. In the early stage, osteoporosis may be absent; later when osteoporosis is at its height, the syndrome may be subsiding. When coarse trabeculation occurs with signs of recalcification the peak of the syndrome is passed. Pain does not parallel osteoporosis: after treatment pain may subside rapidly despite persisting osteoporosis.

2. Treatment. Early appropriate treatment is important; of crucial importance is an understanding of which sensory neuron is affected (DeTakats^{463, 464}). The first neuron lesion, if unrecognized or mistreated, may within 10 to 30 days ascend to the second neuron level and produce the same diffuse intractable dysesthesia with mirror images to contralateral symmetrical areas. The early causalgic state (burning, throbbing pain relieved by suprasystolic compression of limb, by elevation, cooling or moisture) is still localized to the area of stimulation. At this stage the site of trauma (digit, ankle, wrist) should be immobilized and thoroughly infiltrated daily with 1 per cent solution of procaine which blocks sensory stimuli and inhibits secretion of the vasodilator substances. The involved nonmyelinated fibers are more sensitive to procaine than the large myelinated sensory fibers and remain paralyzed even though the anesthesia wears off shortly.

If pain is not relieved, the stimulus has progressed to a higher level as often is shown by spreading neuralgia and osteoporosis. Then repeated block of paravertebral sympathetics is advisable, often with much relief.

Although sympathetic block of itself produces vasodilation, it relieves the painful vasodilation of causalgia because the causalgic type of vasodilation differs from that produced by heat, vasodilators or sympathetic block. The vasodilation with Sudeck's atrophy is not due to sympathetic efferent fibers since sympathectomy not only does not abolish it but increases it. Since sympathetic block helps to relieve the pain of lesions of the second neuron, this pain like that from peripheral traumatic lesions to the lower, first neuron, must be due to a secretion of painful substances which the improved circulation neutralizes. Sympathetic block accelerates blood flow, opens arterioles but constricts capillaries, and gives striking relief despite increased vasodilation. The reflex vasodilation, which is invariably present just after trauma, produces tissue acidity which inhibits destruction of acetylcholine and modifies nervous impulses. Sympathetic block produces a shift to the alkaline side so that acetylcholine is rapidly destroyed. Injections may be required daily or only once a week.

If sympathetic block fails to relieve pain, sympathectomy will be of no value. But if the block promptly abolishes symptoms and they recur with undiminished in-

tensity after a few hours or days, sympathetic gangliectomy should be performed immediately according to De Takats:^{463, 464} for an upper extremity, infiltration or removal, not of stellate ganglion but of second and third ganglia, is required; for a lower extremity, removal or infiltration of the second and third lumbar ganglia.

In late severe cases the spreading neuralgic pain is intractable, may involve shoulder, thoracic wall or opposite limb and may be associated with severe psychoneurosis from unrelieved pain for which psychotherapy is required. For late contractures and ankylosis orthopedic measures are necessary. If local infiltration, peripheral nerve block, sympathetic block and spinal anesthesia fail to give relief, tractotomy at different levels is indicated and DeTakats recommended cutting of spinothalamic tract (anterolateral chordotomy) for intractable lesions of the second level; possibly cerebral tractotomies or removal of sensory cortex for lesions of the third level; "the latter may seem desperate measures" but patients with lesions of the third level become drug addicts, have severe personality changes and often commit suicide and at this third stage neither section of posterior roots nor chordotomy is of value. DeTakats gave the results of these various treatments in 36 cases of "Sudeek's atrophy."⁴⁶⁵

[A newly recognized type of painful osteoporosis with periarticular swelling, which should be known to rheumatologists, occurs as a complication in 2 per cent of hypertensive patients treated with potassium thiocyanate. Eleven cases were recently reported by Hinchey, Hines and Ghormley. Three to six months after such treatment was begun, painful osteoporosis appeared, then mild or moderate dusky periarticular swelling. Feet and ankles were affected most often, a hip, knee or wrist sometimes. One of us, P. S. H., has seen three patients who were referred because of "atypical rheumatoid arthritis." Following discontinuance of doses of the drug recovery began in two or three months, was complete in all 11 cases within five to seven months.—Ed.]

Ganglion. A ganglion is a cystic swelling usually near a joint or tendon sheath which contains thick mucinous fluid. Its lining closely resembles that of joints or bursae. Although bursae are usefully placed, ganglia "have been donated to us by nature as an effect without a known cause." Their origin and nature are in dispute: a ganglion has been considered a rupture of tendon sheath, a retention cyst, a neoplasm, a herniation of tendon sheath or, the more commonly accepted view, the result of cystic degeneration (fibroplasia and colloid degeneration) of connective tissue around, but not inside, the joints.^{312, 1442} Trauma is not a constant etiologic factor. Reportedly 58 per cent of ganglia disappear spontaneously (Cherry and Ghormley³¹²).

Numerous treatments have been used such as breaking the cyst, pressure bandages, injection of sclerosing solution (iodine or carbolic acid), surgical excision, excision and injection of formalin or iodine, aspiration and injection of iodine or iodoform. After any of these methods recurrences may occur. Surgical excisions leave unwelcome scars; even so they are often unsuccessful because of incomplete dissection of the sac. Aspiration and injections must usually be repeated. Cherry and Ghormley³¹² reviewed results, their own and others, from various types of treatment of 104 ganglia on hands or wrists of 102 patients (77 females, 25 males). From all methods good results occurred in 59 per cent of cases but best results were from complete surgical excision.

In 1940 treatment of ganglion by the injection of a proteolytic enzyme (caroid) was recommended. But this treatment in one case resulted in a "surgical tragedy," namely formation of an extensive subcutaneous abscess with widespread necrosis "partly chemical from the enzyme and partly due to the bacteria which it contained." Samples of caroid were found to be "heavily contaminated" with different bacteria. This remedy was strongly condemned by Key.⁹²³

Recently two ganglia were treated successfully by aspiration and injection of Searle's synasol [sodium salts of fatty acids from psyllium seed]; painful reactions

occurred two days thereafter but soon disappeared and the ganglia had not recurred three months later (Van Den Berg¹⁸⁴³).

Juxta-articular Dercum's Disease (Adiposis Dolorosa). Features of adiposis dolorosa are obesity, weakness, nodular tender fatty tumors, neurologic changes and psychic disorders. To the 500 cases already reported was added another case, one with unusual neurologic phenomena, marked muscular atrophy and increase in subcutaneous tissues of legs, severe osteoarthritis of knees (McGavack and Klotz).

Rheumatic Purpura. Special associations between (1) purpura and "rheumatic" symptoms and (2) rheumatic disease and purpura were seen by Davis.^{442, 443} It is well known that patients with various types of purpura often suffer from "rheumatic symptoms" [aching of muscles or joints presumably from small petechial hemorrhages in muscles or synovia—Ed.]. But Davis noted also that patients with various rheumatic diseases (rheumatic fever, rheumatoid arthritis, fibrositis) commonly exhibit purpura. Of 500 consecutive cases of skin purpura 47 (9.4 per cent) were in rheumatic patients; 21 had rheumatoid arthritis, nine osteoarthritis, nine fibrositis, seven rheumatic fever, one acute gout. All but three of the 47 patients were females, suggesting "an endocrine basis."

Davis also studied 88 patients with "hereditary familial purpura simplex"; 79 had purpura simplex, four Schönlein's purpura, two Schönlein-Henoch purpura, two "bruised on trivial injury," and had rheumatoid arthritis and one had pseudohemophilia. Of these 88 patients 60 (68 per cent) had or had had some rheumatic disease as follows: 23 rheumatic fever, eight rheumatoid arthritis, 15 "arthritis distinct from either rheumatoid arthritis or rheumatic fever," "others" (presumably 14) with "severe fibrositic or myalgic pains." In some of the families studied the ecchymoses were traditionally known as "rheumatism bruises."

[The term "rheumatic purpura" is commonly used by dermatologists, rarely by rheumatologists. The matter deserves the further attention of internists, rheumatologists, hematologists and pathologists.—Ed.]

Pellegrini-Stieda Syndrome; Para-articular Calcification at the Mesial Aspect of the Knee Joint. Recent studies did not determine the disputed nature of para-articular calcification at the mesial aspect of the knee joint. Pellegrini (1905) regarded the lesion as a periosteal proliferation or an osseous metaplasia of a ligament. Stieda (1908) considered that it constituted a small detached piece of bone from fracture of the medial epicondyle of the femur. The controversy continues. According to recent writers the condition represents (1) an ossifying epiperiosteal hematoma,¹⁰⁸³ (2) calcification of bursa between the tibial collateral ligament and the capsule superior to the medial meniscus,²⁰⁷ (3) calcified tendon of the vastus medialis,¹⁸² (4) "peritendinitis calcarea," location unspecified,⁵⁸⁴ (5) calcific ligamentitis of the tibial collateral ligament,¹⁶⁹⁷ (6) calcified hematoma in soft tissue close to the medial condyle of femur,¹⁹ (7) calcified hematoma in a heretofore undescribed aponeurotic membrane.¹²⁸⁷

1. Pathogenesis. Acute or repeated trauma was regarded as the usual but not a necessary factor. According to Levinthal¹⁰⁸³ trauma causes periosteal rupture just above or at the proximal attachment of the medial ligament of the knee at the internal condyle of the femur. A hematoma burrows its way between deep muscle fascia and

above the periosteum, connecting with the cortex of bone. The hematoma becomes infiltrated with osteoblasts, and ossifies. Persistent pain is due to "pressure under the underlying structures." The supposed pathogenesis was nicely illustrated diagrammatically.

But Nachlas and Olpp who studied 20 cases clinically concluded that "the condition is not due to a fragment of bone from femur, a tear of periosteum or a calcified bursa." In one patient surgically treated the lesion was in a white fibrous membrane that seemed to invest the medial aspect of the condylar expansion of the knee. On cadavers this was identified as an "aponeurotic layer that hugged the medial aspect of the knee rather closely covering the tibial collateral ligament, the adductor tubercle and the tendon of the adductor magnus." Their 20 cases were in soldiers who despite their general youth, all had associated arthritis (generally osteoarthritis), presumably posttraumatic, and this condition was considered the chief cause of symptoms, not the para-articular ossification which seemed to result from an encapsulated hematoma.

Most writers spoke of the lesion as calcific and some reported spontaneous disappearance of the deposits (Allen¹⁹). But removed specimens showed bony tissue.^{1083, 1287} The calcific shadow is connected to bone¹⁰⁸³ or may be,¹⁹ according to some, but others^{246, 384, 1287} insisted that careful roentgenography always reveals a soft tissue gap between the deposit and bone, which gap is "an essential finding in the diagnosis."¹⁶⁹⁷ In cases in which "the calcification is old, large and attached to bone, it may be confused with a neoplasm."¹⁹ Speed noted a case in which amputation had been done because of tragic confusion with osteogenic sarcoma.

[The orthopedic colleagues of one of us, P. S. H., have studied 52 cases and concluded that the condition represents posttraumatic calcification of the medial collateral ligament. Obviously a variety of lesions have been described under the term "Pellegrini-Stieda syndrome" which is the usual fate of ill-defined conditions given eponymic designations.—Ed.]

2. Treatment. Conservative treatment for the mild pain or tenderness was generally advised. With physical therapy, deposits disappeared in two cases.¹²⁸⁷ Roentgen therapy was recommended.⁵⁸⁴ Surgical excision is rarely required,¹²⁸⁷ but will give relief if conservative measures do not help.¹⁰⁸³ Treatment of the commonly associated arthritis may be more important than that of the calcific lesion.¹²⁸⁷

Aseptic Necrosis of Bone. Any obliterative process which interferes with blood supply to bone may initiate aseptic necrosis. If the necrosis occurs in epiphyseal bone near a joint, secondary osteoarthritis usually results. If the necrosis occurs in the shaft, bone infarcts result. Aseptic necrosis of bone is posttraumatic or nontraumatic. The traumatic type usually affects subchondral bone in one region only, chiefly a hip. The nontraumatic type may affect subchondral bone or shaft and produce multiple or single lesions.

1. Posttraumatic Type. Chief causes of traumatic interference with blood supply to subchondral bone of femoral head were listed as fractures of femoral head, epiphyseal separation, traumatic dislocation and congenital dislocation.¹²⁰ The sequence of pathologic reactions leading to secondary osteoarthritis was outlined (Bergmann; Politzer). Contrary to common opinion aseptic necrosis of femoral head is not always due to interruption of blood supply from the ligamentum teres; in one case proved aseptic necrosis occurred after traumatic dislocation despite the presence of a normal ligament (Kleinberg). Two cases following adolescent femoral epiphysiolysis were noted.¹²⁵⁹

2. Nontraumatic Types. These comprise ones of unknown cause and others related to decompression sickness. Since the aseptic necrosis related to Legg-Perthes' disease or to osteochondritis dissecans often has no apparent relationship to gross or

even to microtrauma, some writers preferred to list it as the nontraumatic variety.^{130, 1396} Politzer also objected to labeling as "osteochondritis" the various necrotic lesions of growth centers since no evidence of inflammation has been found to support the suffix "itis." In such cases the end result (whether or not late disabling secondary osteoarthritis develops) depends largely on the age of the patient at the time of the initial lesion and on the site, whether or not it is a weight-bearing joint. The older the patient and the more weight the affected joint must bear the more likelihood for the development of secondary osteoarthritis.¹³⁹⁰ Aseptic necrosis of a semilunar bone of a child¹³⁹⁶ was reported for the first time.

Aseptic necrosis and bone infarcts commonly affect caisson workers subject to increased atmospheric pressures and the need for controlled decompression. Acute symptoms of faulty decompression ("decompression sickness") are "the bends"; late symptoms which concern bones or joints result from "gas embolism" chiefly nitrogen bubbles. Sites chiefly affected have been long bones and hip or shoulder (Allan). Aseptic necrosis may develop in caisson workers who have not had the "bends" (Taylor^{1779, 1780}).

Aviators flying at altitudes above 30,000 feet may likewise have acute aerobolism, one feature of which is acute pain in joints or bones, sometimes mild, sometimes "excruciating." The pain disappears on descent.^{142, 1721} But no infarcts or aseptic necrosis of bone have been recorded among air personnel.^{1779, 1780}

Osseous and articular lesions identical to those of caisson workers have been found in persons never subjected to abnormal atmospheric pressures or to known trauma. The cause of the aseptic necrosis in such cases is unknown but the vascular interruption has been blamed on fat emboli, bland infarcts, septic foci, peripheral vascular disease. Taylor^{1779, 1780} reported 41 such cases.

Ehlers-Danlos Syndrome. Cases were presented illustrating the three chief features, friability of skin and blood vessels (dermatorrhaxis), overelasticity of skin (dermatocholasia) and overelasticity of joints (arthrocholasia).^{74, 118, 1491, 1743, 1778} In one case creatine metabolism was abnormal.¹³⁹³

Osteopathia Condensans Disseminata. Two cases of this condition (osteopoikilosis: spotted bones) were reported.^{90, 1385}

Osteosclerosis. Cases of osteosclerosis with anemia or nonleukemic myelosis were noted.^{319, 701}

Morton's Metatarsalgia. The cause is now known to be a tumor in the fourth plantar digital nerve (a posttraumatic degenerative fibrosis of the nerve with neuro-matous proliferation). Excision of the tumor relieved all 23 patients.^{61, 1196, 1756}

Arachnodactyly. Findings at necropsy in a case complicated by dissecting aortic aneurysm with rupture were presented with a review of four other reported cases of arachnodactyly and heart disease in which necropsy was done.⁵³⁸

PHYSIOLOGY OF JOINTS, CARTILAGES AND MUSCLES

Joints. 1. Nerve Supply. The nerve supply to articular and periarticular structures was reinvestigated (Smyth and Freyberg).^{608, 1650} Joints are supplied by mixed nerves which innervate also muscles, bones and skin of the same area. No nerve fibers were found in compact bone or cartilage. The nerves terminate as free nerve endings, or in a terminal plexus, or in special nerve organs. The sensory innervation of joints may not derive from the same source as that of overlying superficial areas.

2. Pain. The nature of stimuli causing joint pain was discussed (McEwen; ¹¹⁹⁸ Smyth and Freyberg^{608, 1650}). Smyth and Freyberg¹⁶⁵⁰ found *predictions* of weather (not effect of weather on symptoms) by 20 "arthritic patients" wholly unreliable. [Type of arthritis not stated.—Ed.] The diagnostic indications of pain in various specific joints and the rationale of rest, drugs, local anesthesia, roentgen

irradiation, heat and splints for control of pain were presented. Freezing of skin over joints with ethyl chloride caused disappearance of pain in fractures near joints, stenosing tenosynovitis and low backache (Henry). [The evidence was not convincing.—Ed.]

3. *Motion*. A new hip arthrometer allows recording of a 3-dimension, graphic illustration of hip motions, also minor degrees of limitation of motion.⁶³⁸ A simple useful arthrometer with a fixed horizontal indicator was used by Cooper.³⁷² West used an inexpensive carpenter's boxwood rule as a goniometer. Two new methods of recording joint measurements^{1253, 1989} and another functional classification of joint motions⁴⁵⁵ were described.

Synovial Tissue. Staining reactions with Southgate's mucicarmine stain and metachromic dyes gave no evidence of mucin secretion by synovial cells (Davies⁴³⁶). Metachromasia was only present in "mast" cells along blood vessels. Mitochondria, but not Golgi bodies, were demonstrable in lining cells and the underlying connective tissue cells.

The absorptive function of the synovial membrane in various joint diseases was tested by Efskind with parabrodil and indigo carmine. In hemarthrosis from slight injuries and in "hydrops" of unknown origin there was no change from normal. In "arthrosis deformans" both substances were retained (parabrodil, three to four hours; indigo carmine, 12 to 18 hours). The longest periods of retention occurred in pyarthrosis (12 hours with parabrodil, 24 hours with indigo carmine).

Following intravenous injection in calves, thiocyanate and glucose diffused readily into joint spaces (Zeller, Bywaters and Bauer). Serum and fluid thiocyanate equilibrium was usually attained in one to four hours. The concentration in the fluid averaged 9 per cent lower than that in blood; that in aqueous humor was lower than that of synovial fluid; only traces were present in cisternal fluid.

Synovial Fluid. The viscosity of synovial fluids differs in various joints of the same animal (Davies^{437, 438}). Highest viscosities were found in the axial joints. No histologic differences were found in the synovial membranes to account for differences in viscosity.⁴³⁷ Cell counts were higher in joints of head and neck than in those of extremities. Age and cell count were not related in cattle, but in sheep counts decreased with age. The axial joints showed relatively slight degenerative changes.⁴³⁷

In edematous persons the synovial fluid is increased in amount (Coggeshall, Bennett, Warren and Bauer). Total nucleated cell counts were often increased in fluids from patients dying from varying degrees of (primarily nonarticular) infection. An increase in the absolute neutrophil count was a more sensitive index of synovial inflammation than the total count. The marked synovial tissue reactions in patients with septicemia were of the type seen in early cases of specific infectious arthritis.

Bactericidal activity was demonstrated for streptococci in only 11 per cent of 37 synovial fluids, for *Escherichia coli* in 87 per cent of 39 fluids. The activity for *Escherichia coli* was related to the complement content of the fluid (deGara).

Intra-articular injection of testicular extract reduced the viscosity of synovial fluid in three cases of rheumatoid, and in one case of traumatic arthritis. This change apparently did not result from dilution but from hydrolysis of hyaluronic acid in vivo as the protein content remained relatively constant (Ragan and DeLamater).

That the glycolytic enzymes in synovial fluid are present almost entirely in the leukocytes was shown again (Hubbard and Porter). But two of 14 fluids showed glycolytic activity even after removal of cells. The rate of destruction of glucose added to synovial fluid was at least twice as great as that of fructose.

The "nucleoprotein" of normal joints is digested by normal urine but the urine of rheumatic patients (not defined) loses this power (Freund⁶⁰⁰).

Cartilage. 1. *Chemistry*. The solubility, stability and content of the main poly-

saccharide component, chondroitin sulfate was studied by Hass and Garthwaite.^{790, 791, 792} Calcification of costal cartilage was correlated with decrease in this polysaccharide associated with aging. A histochemical reaction of unknown nature but thought to be specific for cartilage cells was described (Hass⁷⁹¹).

2. *Growth*. Injury to the epiphyseal cartilage plate in young rats and rabbits caused partial to complete arrest of growth; excision of the epiphysis was healed by a transient cartilage which did not contribute to growth (Banks and Compere).

Cartilage from rabbits less than 24 days old, transplanted into the same or other rabbits grew. Cartilage from these young rabbits grew in adult hosts while adult cartilage failed to grow in young hosts (Dupertuis). Autogenous cartilage grafts in dogs remained viable during one and one-half years of observation. Growth was not observed, presumably because the subjects were adult (Gutman and Gutman⁷¹⁸).

The process of cartilage regeneration was observed microscopically by means of transparent chambers implanted in rabbits' ears. Cartilage was formed slowly in relatively avascular regions by motile granular cells of undetermined origin (Clark and Clark).

3. *Aging*. The reported alterations in the articular cartilage (of mice and guinea pigs) due to hormonal and other factors are of particular interest to students of articular disease (Silberberg and Silberberg^{1607, 1608, 1609, 1610, 1611, 1612, 1613, 1614, 1615}). Hypertrophic and retrogressive changes were frequent in normal old mice, but advanced changes were relatively rare.¹⁶⁰⁹ The incidence and severity of articular cartilage lesions were increased by anterior pituitary hormone but apparently decreased by estrogen, testosterone, thyroid and parathyroid hormones. Effects noted were influenced by the age of the animal when the hormone was given.

4. *Metabolism*. The presence of a phosphorylase in calcifying cartilage was reported.^{718, 719} This enzyme, catalyzing the formation of glucose phosphate from glycogen and inorganic phosphate, provides the substrate required by bone phosphatase. In vitro calcification was blocked by agents inhibiting the glycogenolysis except when suitable phosphoric ester substrates for phosphatase were provided.

Injections of potassium iodide into growing mice caused a transient increase in formation of bone and cartilage followed by an accelerated regression (Silberberg and Silberberg¹⁶¹⁶). [The exact significance of these findings is unknown.—Ed.] These effects were qualitatively similar to those following administration of thyroxine or of an anterior pituitary extract. Cell density in bovine cartilage decreases with age. The glycolytic power per cell is undiminished with age but cellular oxidative capacity is progressively reduced, according to Bowie, Rosenthal and Wagoner.^{194, 1507, 1508, 1509, 1859} [The statistical evaluation of the widely scattered and overlapping data is difficult.—Ed.] This reduction in cellular oxidation was attributed to a decline in oxygen activating systems rather than to dehydrogenating mechanisms because of the finding that oxygen consumption in the presence of methylene blue was independent of age.

[The latter conclusion rests on the assumption that the dye provides an excess of activated oxygen and so leaves as limiting factors the mechanisms concerned with oxidation of substrates by removal of hydrogen. Unpublished studies by one of us, W. B., indicate that the methylene blue reaction has nothing to do with tissue respiration.—Ed.]

Muscles. Recent contributions to the physiology of muscles (¹⁶⁹ references) were reviewed by Solandt. Earlier claims that gelatin feeding markedly increased the amount of work performed by male subjects were not supported (Karpovich and Pestrecov). The disturbed creatine metabolism present in certain neuromuscular diseases of man was not improved by the administration of vitamin E,^{1238, 1559} vitamin B₆ (pyridoxine) or ascorbic acid.¹²³⁸ Vitamin E plays an

essential part in the metabolism of skeletal muscles in all species of mammals so far investigated but its importance in the nutrition of human muscle is still uncertain.

OTHER STUDIES ON JOINTS AND RELATED TISSUES

Arthritis in Animals (Naturally Occurring). "Joint-ill" is a form of suppurative polyarthritis in young lambs, caused by alpha hemolytic streptococci, Lancefield group C. Infective endocarditis was present in animals spontaneously or experimentally infected (Blakemore, Elliott and Hart).

"White scours," a polyarthritis of young equine or bovine animals, is said to resemble rheumatoid arthritis and is thought to be due to a filtrable virus. Its early articular lesions were studied by Goldberg.⁶⁶² Earliest changes in cartilage were a surface "blister" and blood vessels budding into cartilage: in synovium, hyperemia and minute hemorrhages. Later features were synovial pannus growing over cartilage, thinning and dissolution of cartilage and its replacement by granulation tissue, villous and papillary overgrowth of synovium with perivascular infiltration of lymphocytes and plasma cells.

The spontaneously occurring suppurative arthritis of rats and mice due to pleuropneumonia-like organisms was studied further. The strains recovered by Preston¹¹¹¹ appeared identical with that described by Klieneberger (1938) as "L 4." A strain of the pleuropneumonia-like group recovered from a rat spontaneously affected was identical with one recovered from rats inoculated with material from a patient with acute rheumatic fever. Admittedly the latter strain might have been of rat, rather than human, origin (Beeuwkes and Collier).

Experimental Arthritis. This can be produced by many different agents listed by Westcott.

1. *Bacterial.* Arthritis in rats and mice was produced by injections of various strains of pleuropneumonia-like organisms^{1106, 1111, 1112} and was generally fatal.¹¹⁰⁶ The suppurative arthritis produced resembled human pyogenic arthritis rather than rheumatoid arthritis.¹¹¹¹ The arthritis in rats could be prevented^{1106, 1111} or notably minimized by injections of myochrysin given with or shortly after the infective dose. Also similar arthritis in mice was cured by various gold, but not by sulfur, compounds (Preston, Bloek and Freyberg¹¹¹²), penicillin (Powell and Rice¹¹⁰⁶), neoarsphenamine, bismuth, salicylates or sulfapyridine (Sabin and Warren^{1521, 1525}).

Rabbits sensitized to products of hemolytic streptococci often developed synovial reactions after intravenous injections of homologous culture material (Angevine, Cecil and Rothbard).

Experimental hemolytic streptococcal arthritis in rats was prevented but not cured by myochrysin (Rothbard, Angevine and Cecil) but the prophylactic dose was close to the lethal dose. Purulent arthritis was produced in rabbits by intravenous injections of *Staphylococcus aureus* (Rigdon). A strain of *Streptobacillus moniliformis* from a patient with rat bite fever was used to produce infection of chick embryos; invasion of blood stream and almost exclusive localization of the infection to synovium occurred (Buddingh).

2. *Hormonal.* Polyarthritis was produced in adrenalectomized or thyroidectomized female albino rats by overdosage with desoxycorticosterone (Selye, Sylvester, Hall and LeBlond). The incidence of arthritis was higher if the animals were exposed to cold. The polyarthritis histologically resembled that of acute rheumatic fever and was often associated with Aschoff bodies. Selye and Pentz¹⁵⁵⁷ also reported the occurrence of rheumatic carditis, periarteritis nodosa and nephrosclerosis following the administration of large amounts of desoxycorticosterone in unilaterally nephrectomized rats. The authors concluded that the pathogenesis of rheumatoid

arthritis, rheumatic fever and periarteritis nodosa may be related to adrenal insufficiency.

[These results are as yet unconfirmed by other workers. Further studies are needed to eliminate the possibility of spontaneously occurring arthritis due to streptobacilli or pleuropneumonia organisms in the rats.—Ed.]

3. *Chemical*. Intra-articular injections of silver nitrate produced acute arthritis and subsequent atrophy of adjacent muscles. The atrophic muscle revealed abnormal synaptic behavior and was resistant to curarization. Prostigmine produced less potentiation and more depression in the "arthritic" than in normal muscles.⁶¹⁸

Articular Roentgenography. To discover traumatic lesions of knees not demonstrable in conventional views, special views to demonstrate the intercondylar notch and certain aspects of the patella were advised.²⁸⁴ Technics for improved visualization of lumbosacral junction³⁹⁰ and the foot⁶²⁶ were described. Widening or obscuring of the obturator shadow was valuable in early roentgenographic diagnosis of septic hip disease.⁸⁰⁸ "Pneumoroentgenography" was advocated in cases of persistent knee disability.^{161, 414, 795, 1675}

RHEUMATIC DISEASES AND THE WAR

Influence of War on the Incidence of Rheumatic Diseases among Civilians. During wartimes in the past the *general* health of the people behind the lines has, paradoxically, improved. During World War II this was again generally true in countries which maintained their freedom. But the incidence of certain diseases did not follow the general pattern of improved health. In Great Britain the incidence of acute rheumatic fever declined notably but that of chronic rheumatism increased, presumably for the following reasons: "Many people previously employed in light work are now engaged in much heavier tasks. The housewife makes munitions; the woman factory worker does work previously performed by men. 'Digging for Victory' bringing into action muscles long disused, can be another promoting cause of rheumatic trouble if early indications are neglected. It is well recognized that in a certain proportion of cases of rheumatoid arthritis the onset of the disease follows a shock."⁸⁶⁶

[No actual figures on the incidence of chronic rheumatic diseases were given.—Ed.]

In Great Britain the incidence and severity of acute rheumatic fever, steadily declining before the war, fell at a "greatly accelerated" rate during the war; its death rate was halved. This wartime decline resulted presumably because of a decrease in poverty owing to abundant employment, the feeding program (milk, solid food) for school children, the "long changes of air" (country life) due to evacuation from cities, and perhaps "a change in the relationship between man and the *Streptococcus pyogenes*" (Glover).

Influence of War on the Incidence of Rheumatic Diseases among Military Personnel. Based on previous experiences a high incidence of rheumatic diseases among American¹³⁷⁸ and British military personnel^{526a} was expected. "Apart from other conditions of service, the intensive development of mechanized warfare will make them subject to conditions known to be specifically productive of rheumatic disease in industrial life—frequent small bruising and tearing injuries, working in cramped conditions, frequent alterations of heat and cold."^{526a}

To what extent this expectancy was borne out cannot yet be stated precisely since the figures on incidence are just now being compiled. But certain generalizations can be made from the data under review.

Relation of Rheumatic Diseases to War. In their relationship to war "rheumatic diseases" can be divided thus: (1) those peculiar to war and military service, (a) infected wounds of joints (septic and traumatic arthritis), (b) traumatic lesions of joints and related structures caused by noncombat trauma of a military type (long marches, mechanized warfare, paratroop injuries), (c) rheumatic diseases related to military herding (epidemic rheumatic fever; articular complications of scarlet fever, meningococcic or streptococcic infections), (d) lesions induced by excessive (military) exposure to cold and wet, (e) articular diseases arising from the location of troops in certain regions (epidemic tropical acute polyarthritis; "epidemic" coccidioidomycosis); (2) those coincidental to war and military service, (a) recurrences or exacerbations of pre-existing rheumatic fever, rheumatoid arthritis, fibrositis or gout, favored perhaps by military life, (b) appearance of certain rheumatic diseases, rheumatoid arthritis, osteoarthritis, fibrositis, nonepidemic rheumatic fever, while the soldier was under no *special* military stress (in camp or not in zone of combat), (c) articular complications of venereal diseases.

Somewhat to their surprise and "disappointment" American rheumatologists who entered military service saw relatively little articular diseases specifically related to war (septic arthritis from war wounds, or rheumatic diseases specifically induced by fighting under battlefield conditions of cold and damp). The "rheumatic diseases" of World War II were of a more prosaic kind and comprised four chief conditions: epidemic rheumatic fever among military personnel in certain training areas; psychogenic rheumatism; the ever-present and ever-developing rheumatoid arthritis, particularly spondylitis, and musculoskeletal lesions related to trauma. Of much less importance statistically, though sometimes of greater academic interest, were all the other conditions encountered.

Articular Diseases Peculiar to Military Service. 1. Wounds of Joints. Early in World War I wounds of joints commonly resulted in sepsis, amputation and death, sometimes a stormy convalescence and recovery with ankylosis (Anderson²⁵). Later developments in treatment improved the outlook materially, but even so wounds of joints still posed a potentially serious problem in the early years of World War II. Thus among 237 wounds of knee in the British Libyan Campaigns (1941-1942) suppurative arthritis resulted in 35 per cent; amputations were required in 4.4 per cent; death occurred in 2 per cent.²⁶⁰ Fortunately the use of better techniques, the availability of sulfonamides and the development of penicillin changed matters completely so that later wounds of joints often produced no significant sepsis and when septic arthritis did develop, it was handled so well in forward echelons that septic arthritis and its results became a negligible factor in general hospitals and rheumatism centers in the zones of the interior. Thus in 1944 results in 101 cases of wounds of the knees were as follows: normal knees in 75, "useful knees" in 15, stiff knees in 11; no deaths, no amputations.²⁶⁰

The general management of wounds of joints was outlined. Front-line surgery included (1) preliminary treatment of shock and sepsis, (2) "surgical toilet" of wound, (3) sulfonamide-dusting, (4) vaselin gauze without closure, (5) splinting, (6) evacuation. Later treatment at an evacuation hospital usually included arthrotomy for débridement (removal of fragments of bullet, bone and cartilage), excision of devital-

ized skin and other tissue, sometimes aspiration or irrigation of joint cavity, local and general use of sulfonamides or penicillin, closure of articular cavity as early and completely as possible, immobilization by "closed plaster" or splint. "After-treatment" included such aspirations, secondary arthrotomies, redressings, sequestrectomies and other orthopedic procedures as necessary.^{25, 101, 137, 138, 140, 260, 408, 521, 621, 689, 1009, 1124, 1140, 1141, 1314, 1420, 1653, 1867, 1870} Emphasized was the value of early treatment to prevent or minimize sepsis and destruction of cartilage. "Send the surgeon up to the patient, not the patient back to the surgeon."¹¹⁴¹

2. *Lesions from Noncombat "Military Trauma."* Internal derangements of knees resulted from training exercises, camp sports and other noncombat trauma. Results of elective surgery were disappointing and such surgery was officially discouraged except in selected cases.¹⁸⁶⁸ In such cases surgery was often followed by the patient's return to full duty.^{279, 299, 1000, 1689, 1930} Special roentgenography aided in diagnosis.^{284, 795, 1675} Cases of osteochondritis dissecans^{286, 329} and Pellegrini-Stieda syndrome among soldiers^{1287, 1697} were noted. Traumatic tenosynovitis and bursitis of feet and legs affected infantry troops^{444, 916, 947}; suprapatellar tenosynovitis affected certain bomber pilots.³⁶⁹ Cases of herniated nucleus pulposus were common among soldiers. In general operations were performed only for those which resulted from military service.^{798, 1688} In selected cases surgical results were as satisfactory among soldiers as among civilians (Haynes⁷⁹⁸; Robertson and Peacher¹⁴⁷⁴; Spurling and Thompson¹⁶⁸⁸; Spurling and Scoville¹⁶⁸⁷). Cervical as well as lumbar disks were affected.¹⁶⁸⁷ Medical officers assisted in the development of pantopaque myelography.^{36, 117, 886, 494, 498, 647, 1555, 1678} Certain cases of "military lame back" were ascribed to faulty posture.¹⁷⁹⁵

3. *Rheumatic Fever Related to Military Herding.* In the section on "Rheumatic Fever" were discussed the "epidemics" of acute rheumatic fever which affected military personnel in certain American army and navy training centers situated mostly in the "rheumatic fever belt" north of 35 degrees of latitude, especially in the Rocky Mountain and Great Lakes regions. Most affected were those in army camps in Colorado and Wyoming, naval stations at Newport and Great Lakes.^{704, 856, 1182, 1174, 1176, 1919, 1969} Certain American troops on hospital ships being evacuated from tropical South Pacific regions were likewise affected.¹⁶⁸⁶ British naval recruits at certain training centers were affected.^{691, 692, 693, 694, 967} Observations on rheumatic fever among British troops isolated at a remote desert camp in Burma, among troops in the Middle East (Kersley⁹⁸⁹), and among recruits and civilians in Malta were also made.^{379, 1819}

So numerous were the cases in American camps in 1942 and 1943 that special measures were taken. The Army Ground Forces instituted researches under two special commissions.¹⁴⁷³ The Army Air Forces set up a rheumatic fever control program with convalescent centers in regions relatively devoid of streptococcic respiratory infections.^{532, 855, 999, 1454, 1815, 1910} Research units were established by the navy.^{331, 1885, 1886, 1920} Canadian medical officers also studied the problem.^{547, 757} New methods of treatment were tried out by army and navy medical officers. Penicillin was found to be ineffective.^{269, 578, 1432, 1884} Large doses of salicylates given intravenously were recommended,³³⁰ but later found to be not superior to older methods of salicylate administration. Most effective was sulfonamide prophylaxis carried out extensively among army^{855, 1074} and naval personnel.^{294, 331} Promising results also were obtained by control of airborne infection in army camps by special care of barracks and bedding, use of aerosols and others.¹⁴⁷³

Studies on the incidence of rheumatic heart disease among candidates for military service were made.^{1090, 1514}

4. *Other Infections Related to Herding.* The relation of epidemics of scarlet fever to rheumatic fever were studied; most of the articular complications of scarlet

fever were regarded as precipitated attacks of rheumatic fever, not true scarlatinal arthritis.^{1885, 1886}

Relatively minor epidemics of meningococcic infections affected American,^{431, 1158, 1498, 1738} Canadian,⁴⁶⁷ and British³⁷⁵ troops. The prophylactic measures used against other air-borne infections practically eliminated these also. Articular complications of meningococcic meningitis or of meningococcemia without meningitis were fairly common and at times resembled acute rheumatic fever. Response of the articular lesions to sulfonamides was often, but not always, satisfactory. Penicillin was promptly effective in some cases,¹³⁷⁵ but not in others.¹¹⁹⁵

Small outbreaks of epidemic pleurodynia (Bornholm disease) affected American,¹¹⁹² British,¹⁹²⁶ and New Zealand¹² military personnel.

5. *Articular Diseases Encountered in Special Localities.* Epidemic acute tropical polyarthritis, a "new" rheumatic disease, was discovered among Australian and American troops in the Northern Territory of Australia and on adjacent islands. As noted elsewhere, its recognition and description were entirely the work of medical officers. The excellent character of these studies does credit to those concerned and shows that original work can be done by alert medical officers even in the field with meager laboratory facilities.^{742, 775, 811, 1270, 1695}

The articular complications of acute primary coccidioidomycosis ("desert rheumatism") often escape precise diagnosis. Coccidioidomycosis is chiefly endemic in the San Joaquin Valley of Southern California. During the war, troops were concentrated for training in certain areas not known to be infected. A small number of cases (about 200 reported) of acute, and some (about 55 reported) of chronic (granulomatous), coccidioidomycosis resulted.^{160, 671, 672, 1190, 1595, 1925} The military implications having been appreciated, a control program was set up.¹⁶⁰

Rheumatic Diseases Coincidental to War and Military Service. 1. *General.* Studies on the total and relative incidence of rheumatic diseases among American and British troops indicated that the overwhelming majority were cases coincidental to, rather than resultant from, military service. Among armies (as among civil populations) totaling several million men, thousands of cases of acute or chronic rheumatism were bound to develop regardless of war. "Recruits are generally healthy people, but a certain number will have inherited a rheumatic diathesis and be liable to develop rheumatism especially after exposure or strain."¹²⁹⁸ Military service undoubtedly provided certain predisposing or aggravating factors (which sometimes operated earlier or more potently than might have occurred otherwise) but most of the rheumatic diseases encountered would have developed whether their victims were in "civies" or in uniform.

In World War I "chronic arthritis" (presumably mostly rheumatoid type), rheumatic fever, muscular rheumatism and gonorrheal arthritis (in the order named) comprised the bulk of rheumatic diseases among American troops.^{816, 817} In World War II American troops were chiefly affected by muscular rheumatism, "tenosynovitis or synovitis," rheumatoid arthritis and rheumatic fever. Much of the muscular rheumatism, tenosynovitis and rheumatic fever cleared up. Those rheumatic soldiers who did not improve but were sent to the army's five rheumatism centers generally had rheumatoid arthritis, psychogenic rheumatism, residues of rheumatic fever, or chronic muscular or capsular rheumatism (fibrositis).^{173, 176, 816} Compared to American experiences the diagnosis of "fibrositis" was made four to five times as often among British troops; the reported incidence of rheumatoid arthritis was less than half that among American troops and "psychogenic rheumatism" was either rarely encountered or rarely recognized or diagnosed as such.^{820, 959, 1541}

[These differences probably represent differences in diagnostic criteria and standards.—Ed.]

2. *Miscellaneous Observations.* Among rheumatoid soldiers the ratio of spondylitis to arthritis of peripheral joints was unusually high—1:3 or 1:2 as compared to the proportion of 1:6 or 1:13 among civilians.^{173, 176, 816, 1408, 1599} Although few in number, most of the recently reported cases of Reiter's syndrome were among soldiers.^{637, 858, 1504, 1599}

As already stated American soldiers with "psychogenic rheumatism" provided a real problem on the "psychiatric" and "rheumatism services" of general hospitals and at the army's rheumatism centers.^{144, 174, 581, 631, 748, 816, 1531, 1544, 1905} Such cases comprised 15 to 20 per cent of "rheumatic cases" at rheumatism centers.⁸¹⁶ Only one Canadian⁸⁰² and two British reports^{524, 571} have been noted.

Despite an increased incidence of gonorrhea among military personnel, the incidence of gonorrheal arthritis, thanks to chemotherapy, fell remarkably, to as low as 0.1 or 0.3 per cent.¹⁸²⁶ In most of the few reported cases prompt cure occurred if enough penicillin was given.^{413, 754, 815, 816, 928, 1790} The supposed "gonorrheal arthritis resistant to penicillin" seen at one rheumatism center appeared in most cases to be rheumatoid arthritis precipitated, reactivated or notably aggravated by acute genital (not articular) gonorrhea.⁸¹⁶

The studies in the following list made by medical officers or others, pertaining to articular or rheumatic conditions among soldiers, have been referred to in the appropriate parts of this Review: unusual articular diseases (palindromic rheumatism)¹⁷⁹³; articular symptoms of periarteritis nodosa^{1183, 1184}; of decompression sickness¹⁷²¹; dermatomyositis¹⁶¹⁷; psoriatic arthritis⁵⁸⁹; tumors of joints,^{109, 329} tabetic neuroarthropathy,¹⁹⁰⁰ articular reactions to penicillin [the first reported case⁶⁸¹—Ed.], or to sulfonamides¹¹⁵³; certain clinical investigations^{63, 175, 377, 382, 384, 548}; miscellaneous reports.^{573, 853, 1099, 1127, 1343, 1991}

THE CAMPAIGN AGAINST RHEUMATISM

In every country surveyed the same findings have been made: (1) rheumatic diseases outranked all others as a cause of chronic morbidity; (2) rheumatic diseases annually involve each country in great expense; (3) adequate facilities for the care of most rheumatic patients are nonexistent. In the United States as elsewhere the total army of rheumatic victims is relatively neglected. Compare their prospects with that of others, for example, the tuberculous: for our 680,000 tuberculous patients there are available about 100,000 free beds and \$100,000,000 for care and research. But for our 6,850,000 rheumatic patients there are available only about 200 free beds and \$200,000 for care and research. In other words although there are 10 times as many rheumatic as tuberculous patients the latter have available 500 times more beds and money. Thus the tuberculous patient, happily thereby a "vanishing race," receives 5,000 times as much attention as the nonvanishing rheumatic.

A recent survey of American voluntary health agencies (Buell²⁵⁰; Dublin⁴⁸⁵; Gunn and Platt⁷¹⁶) disclosed an astonishing paradox: "The greater the need the less the public's support." But as it concerns the menace of rheumatism, this is true only because the American public has not been sufficiently informed or aroused. Once enlisted, public opinion has given generous support as shown by data in table 4. Physicians concerned with rheumatic diseases, only want more financial support for these patients, not less for others.

The same situation prevails elsewhere. In England and Wales before the war there were 30,000 beds for tuberculous patients, only 1,000 for the rheumatic (Ellman⁶²³). Yet "rheumatism" costs the people of England and Wales over

TABLE IV
Disease Prevalence versus Voluntary Public Support

Disease	Support	Amount Collected Annually	Patients	Dollars Available per Patient
Infantile paralysis	Sold to public	\$16,600,000	175,000 crippled	94.00
Tuberculosis	Sold to public	15,000,000	680,000	22.00
Cancer	Partly sold to public	4,000,000	500,000 under treatment	8.00
Diabetes	Not sold to public	30,000	660,000	.05
Heart disease	Not sold to public	100,000	3,700,000	.03
Rheumatism and arthritis	Not sold to public	?	6,850,000	?

For tuberculous patients: 100,000 free beds; \$100,000,000 available for care and research.
For rheumatic patients: 200 free beds; \$200,000 available for care and research.
"The greater the need the less the public's support."

25 million pounds annually,^{864, 865, 866} and constitutes "the greatest single enemy of social well being and economic efficiency in Great Britain."^{826b} From Scotland the Medical Advisory Committee¹²¹⁵ reported that rheumatism, especially the muscular type, constituted "a major health problem in Scottish industrial life" and caused more days of incapacity than any other group of diseases. In Sweden where most workers are insured, rheumatic cripples become pensionable and were doing so at the rate of 5,000 each year. Although treatment facilities there are reportedly the best in Europe, "the great majority [of patients] are not well looked after" (Copeman³⁸¹; Sundelin).

The war interfered with notably, where it did not stop entirely, the campaign against rheumatism. But the activities of the American Rheumatism Association and the British Empire Rheumatism Council, though seriously curtailed, were continued in part. In lieu of national meetings, prevented by transportation and other difficulties, sectional programs were held by local affiliates of the American Rheumatism Association. New local groups have been formed and there are now rheumatism societies in such cities as New York, Philadelphia, Chicago, Washington, D. C. The membership of the American Rheumatism Association is now more than 400. Prior to 1910 there were no special rheumatism clinics in the United States; now there are scores, 27 in New York City alone (Snyder and Traeger¹⁶⁶³). Each year several universities and the American College of Physicians have sponsored short postgraduate "refresher courses" on rheumatic diseases. During the war many American physicians with a special interest in rheumatic diseases entered military service; the military authorities wisely took advantage of their special interest and were able to assign most of them to appropriate duties so that certain clinical studies were continued. In the United States the local groups are coördinating their fund-raising efforts with those of the American Rheumatism Association to the end that plans for a unified national campaign have been made.

The Canadian Rheumatism Association was formed in 1936; a number of its members belong also to the American Rheumatism Association and the two organizations enjoy a most cordial relationship. Several Central and South American countries have flourishing rheumatism associations, notably Argentina,

Brazil and Mexico. To correlate their efforts and interest, the Pan-American League against Rheumatism was recently formed (Pemberton¹³⁶³; Swaim¹⁷⁵³).

In Great Britain despite great difficulties the activities of the Empire Rheumatism Council were continued under the vigorous leadership of Lord Horder.⁵²⁶ By him and his colleagues much was accomplished as is well shown in the Council's stimulating annual reports.⁵²⁶ The Council's long-range objective is to see to it that all rheumatic patients shall have available treatment appropriate to their needs. The Council has the Government's assurance that rheumatic patients will be fully provided for in its developing scheme for social medicine. Most of the funds required for this exceedingly ambitious program will come from Government. A "blue-print for national action" against the "social plague of rheumatism," prepared by Horder,⁸⁶⁴ has been well received as a basis for discussion, "to bring the issue into the region of practical medical politics."⁸⁶⁵ It involves eventual plans for the establishment of Regional Centers for Special Treatment and more numerous local centers, and immediate plans for post-graduate courses on rheumatic diseases, of lengths from one to several months. A prospective syllabus for such a course was drawn up (Abrahams⁴). The Council's survey of the value of current remedies led to the conclusion that thereby about 60 per cent of rheumatic patients "get a cure or substantial relief if given the right treatment at an early stage and this without serious disturbance of their industrial or domestic life."^{526c} The Council subsidized 20 research projects, a chief one being a study on the causes of the high incidence of rheumatic fever in training establishments of the Royal Navy. While fostering national action the Council meantime has encouraged the establishment of new treatment centers in civic, university and industrial hospitals. Its publication, the *Annals of Rheumatic Diseases*, survived the war as the only European journal dealing specifically with the problem of rheumatism; it is now published quarterly as a supplement to the *British Medical Journal*. Using to date only private funds, the Council expended about \$250,000 thus: for research 38 per cent, for treatment 36, for educational propaganda 15, for administration 11. As part of its program the Council investigated the value of 256 bona fide therapeutic suggestions sent from all over the world; but it refrained from such studies as the investigation of a certain species of apple (grown by the correspondent) which was "an infallible cure for all forms of rheumatism"! Above all the Council has effectively aroused British public opinion, "the controlling force of official action." By joining forces with the British Orthopaedic Association the Council has ensured a united front of medical rheumatologists and orthopedists on problems affecting the rheumatic patient.

In Scotland^{435, 1215} and in Sweden³⁸¹ somewhat similar plans for governmental action have been drawn up. The Scottish plan recommended that the central units should not be isolated rheumatism centers but should be part of large teaching general hospitals. In Sweden certain beds in county general hospitals are to be devoted exclusively to rheumatic patients.

The Ligue Internationale contre le Rheumatisme, dormant during the war, has been revived under the leadership of Drs. Ralph Pemberton (its President), Van Breemen and others, and will hold its first postwar international congress in the United States in June, 1949.

It is interesting to compare the American and British campaigns. In this

country the emphasis has been on the improvement of voluntary community effort to be directed and unified in part by a national, but nongovernment, agency (currently the American Rheumatism Association). Thus chief reliance is placed on the contributions of individual physicians or small groups in the field of treatment and research. These "cells," working "from the bottom," often have been made up of individual members of the American Rheumatism Association who are thus making their all-important personal contribution to the national effort. But in Great Britain greater emphasis is on national action, the Government to be chiefly responsible for the financial support and organization of effort. Excepting the Heberden Society, composed largely of London rheumatologists, there is no British Rheumatism Association, no unification of the British medical profession interested in the problem. In its place the small potent Empire Rheumatism Council is the motivating force "from the top." Both campaigns are far from their goal. The weaknesses of voluntary effort are glaringly apparent^{250, 485}; the potential weaknesses of governmental action and "socialized medicine" have been pointed out but cannot be fully defined until action has occurred. Each group of campaigners can learn much from the other. Contrary to the usual adage it might be well for each country to "light the candle at both ends." Thus the United States should step up its national campaign to arouse public opinion, first for strong community effort, later as necessary for supplementary governmental support consistent with the American desire. Thus Great Britain, having achieved its government's commitment for (future) national action, might well establish a British Rheumatism Association to be the main force by which national action is applied to the individual.

Regardless of details the international campaign is proceeding and is succeeding modestly. To "rheumatology" more and more physicians are devoting much or all of their time. But for full success the public must support these physicians. It is not correct to say that the public gets only what it wants or deserves and that if the public really wanted a cure for rheumatism or cancer it could obtain it by adequate support. Even with the latter the public could hardly "buy" the remedy in a year or a decade. But unfortunately much of the rheumatic public ignores the useful remedies now available. Individual initiative being what it is, the public has largely received benefits it did not request. It did not ask for the telephone, automobile or radio. But for good or ill it got them. Thus national action is largely of value as it enhances the opportunities of the individual worker and utilizes his contributions. To that all important end united effort must be obtained.

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CASE REPORTS

ACUTE THROMBOCYTOPENIC PURPURA DUE TO NEO-ARSPHENAMINE: REPORT OF A CASE WITH EXAMINATION OF THE MARROW *

By PAUL G. HATTERSLEY, M.D., *San Francisco, California*

ACUTE thrombocytopenic purpura is a well known complication of the arsenical treatment of syphilis. Although occurring rather rarely, it is the most common of the blood dyscrasias arising from the use of the arsphenamines, and it has been seen at least once in most clinics where sizeable numbers of luetics are treated. The disorder usually occurs after a number of doses of the drug have been given, although it may follow the first injection. It is characteristically acute in onset, and often is preceded by a nitritoid type of reaction immediately after injection. The platelets may entirely disappear from the peripheral circulation, but usually begin to reappear within 24 to 48 hours, and return to normal levels within four to seven days. Recovery is the rule unless there is the complication of agranulocytosis or aplastic anemia.

Much has been written concerning the mechanism of production of thrombocytopenia. It is well known, of course, that in agranulocytosis and aplastic anemia due to the arsphenamines there is depression of the bone marrow. Some writers have logically assumed that in thrombocytopenia there is likewise a selective injury to the megakaryocytes in the marrow.¹ It is more commonly believed, however, that the platelets are destroyed in the peripheral circulation,^{2,3} or are pooled in dilated capillaries.⁴⁻⁸ It is apparently felt that the short course of the disease and the prompt reappearance of platelets in the blood speak strongly against the possibility of marrow injury.⁹

It is surprising, considering the apparent conviction with which such views are stated, to find in the literature only three brief references to actual examination of the bone marrow during the course of the disease. Falconer, Epstein and Wever⁴ describe the marrow of a single case as follows: "A few megakaryocytes were observed on the film, but in a differential count of 500 cells none were found. Both the erythroid and the myeloid elements of the marrow apparently had been stimulated." The differential count of the marrow is not included in their report, and nothing is said regarding the morphology of the megakaryocytes. They apparently did not consider the decrease of these cells significant.

Corrie¹⁰ reported the marrow of a single case as showing the "picture of blood regeneration." The differential count on his case was fairly normal, but he made no mention of the number or morphology of the megakaryocytes.

The most complete report is that of Schwartz and Vander Heide⁸ who describe the marrow of their case as "entirely normal; the megakaryocytes pres-

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From the Department of Medicine, Stanford University Medical School.

ent appeared of normal structure, staining quality and number." The specimen in this case was obtained on the ninth day of the disease, however, well after recovery had started. It is questionable whether it represents the picture during the height of the disease.

It is evident, then, that until there have been more adequate marrow studies, it will remain impossible to say with assurance whether there is marrow injury in this disorder or not. It is in an effort to begin to answer that question that the present case is reported, with observations on the sternal marrow.

CASE REPORT

K. J., 18 year old Negress, came to the Stanford syphilis clinic on August 20, 1943 for treatment of her latent syphilis which had been discovered on a routine Wassermann examination.

Her father had died of paresis six years before, but her blood, and that of her mother and brother, had been negative at that time. She knew of no primary lesion, but had been treated for several months for a pelvic discharge. There was no history of bleeding tendency. Physical examination at the start of treatment was negative except for hypertrophied tonsils. The bleeding time was normal (3 minutes by Duke method).

Anti-syphilitic therapy consisted of two courses of 10 weekly intravenous doses of neoarsphenamine, each of 0.45 gm., alternating with two courses of intramuscular Sobisminol, each comprising 20 doses of 0.03 gm. The Wassermann test reverted to negative, and the only untoward reaction from the treatment, about which she said nothing at the time, consisted of brief spells of headache and diarrhea following the last few doses of neoarsphenamine.

The third course of neoarsphenamine was started on January 16, 1945 without reaction. The second dose on January 30, however, was immediately followed by a rather severe bout of coughing, sub-sternal distress, nausea, vomiting and chills. She returned home, where vomiting was followed by diarrhea. Twelve hours after the injection, moderately profuse epistaxis began, accompanied by oozing of blood from the gums and small reddish spots on the lips, face and extremities. She entered Stanford University Hospital 36 hours later for study, although by the time of entry she had already begun to feel better, and the bleeding had stopped.

Physical examination on entry showed a fairly robust mulatto girl with a few fading purplish petechiae over her face, thighs and legs. There was a small sub-conjunctival hemorrhage on the left, but the eyes were otherwise negative and the ocular fundi were clear. There was fresh clotted blood in the nares and posterior pharynx, and oozing from the gingival margins. There were hemorrhagic spots on the lips and petechiae scattered over the palate. The tonsils were large and ulcerated. A few firm, non-tender sub-mandibular lymph nodes were palpable bilaterally, but there was no other glandular enlargement. The heart and lungs were clear. The spleen and liver were not palpable, and there was no abdominal tenderness. The extremities were negative except for petechiae. The reflexes were in order.

Blood count on entry showed severe thrombocytopenia and a rather marked shift toward immaturity in the granulocytes (table 1). There was no anemia, and no primitive cells were found. Clotting time was normal (3½ min. by Lee-White method) but bleeding time was much prolonged (21 min. by Duke method) and clot retraction was very poor. The tourniquet test produced a heavy sprinkling of petechiae. Urine and stool contained no blood.

Sternal puncture the next day (February 2, 1945) yielded a cellular marrow (table 2) which was abnormal in two respects: (1) There was a complete absence

TABLE I
Case K. J., Blood Counts

	2-1-45	2-2	2-4	2-5	2-6	2-8	2-21
Erythrocytes	4.25 M	4.71			4.12	4.06	4.43
Hemoglobin, gm. %	13.6	15.0	14.4			13.8	
Leukocytes	10,100	10,400	10,200	10,500		15,400	13,500
Neutrophiles	76%	37%	28	50		72	47
Segmented	38	28	20	42		58	43
Banded	30	9	6	8		14	4
Myelocytes	8	—	2	—		—	—
Eosinophiles	—	1	—	—		—	5
Basophiles	1	—	—	—		2	1
Lymphocytes	22	59	70	48		25	46
Monocytes	1	2	2	2		1	1
Platelets	42,000	28,000	20,000		58,000	191,000	248,000
Bleeding time		21 min.				2½ min.	

of megakaryocytes and of platelets, but a marked increase in megakaryoblasts, many of them showing signs of degeneration; (2) there was a moderate shift toward immaturity in the granulocytes, with very few segmented neutrophils, and an increase in early myelocytes and myeloblasts. The erythroid series appeared entirely normal.

The fact that recovery was extremely likely was recognized, but in view of the persistence of the thrombocytopenia, an increasing neutropenia, and the rather alarming myelogram, it was decided to use BAL, the new arsenic antidote which had recently been made available. Consequently, on the fifth day of the disease, she was given four doses of 0.225 gm. intramuscularly in peanut oil at four hour intervals, and subsequently 0.150 gm. daily for four days. These injections were tolerated without any untoward reaction except for a few minutes after the second, when a "prickly" sensation spread from her face to the rest of her body, accompanied by a feeling of "shakiness" and anorexia, all clearing within an hour.

Clinical improvement continued from the time of entry, with prompt and complete disappearance of petechiae and bleeding tendency. The menstrual flow, which appeared on the sixth day, was of normal amount and duration. The neutropenia had disappeared by the seventh day after the onset of symptoms, and the thrombocytopenia by the tenth day. A second sternal puncture on the eighth day (February 6, 1945) yielded a marrow which differed from the first in the following respects: (1) Megakaryocytes had reappeared in considerable numbers, and while some were

TABLE II
Case K. J., Differential Counts of Sternal Marrow

	2-2-45	2-6-45
Total granulocytes	72	71
Neutrophiles	63	67
Segmented	7	12
Banded	27	32
Myelocytes	29	23
Eosinophiles	4	2
Basophiles	1	—
Myeloblasts	4	2
Lymphocytes	13	10
Monocytes	1	1
Plasma cells	1	1
Nucleated red cells	13	17
Myeloid/erythroid ratio	5.6	4.2

of the immature types, signs of degeneration had disappeared and many were actively producing platelets; (2) there was a definite shift back toward maturity in the granulocytes.

She was discharged on the twelfth day after the onset of symptoms, apparently well. A blood count on the twenty-third day was essentially normal and there has been no return of bleeding in the 20 months that she has been followed since. Anti-syphilitic therapy was subsequently completed with a third course of intramuscular Sobisminol, and she was put on probation, her syphilis apparently arrested.

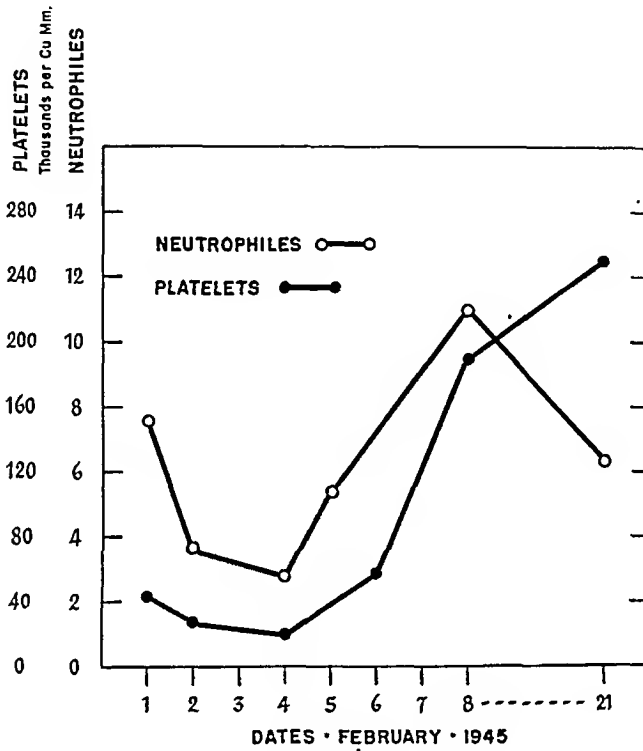


FIG. 1. Neutrophile and platelet counts. Case K. J.

DISCUSSION

This is a fairly typical case of acute thrombocytopenia following neoarsphenamine therapy of syphilis. It is characteristic in that it appeared late in the course of treatment, was ushered in by a nitritoid reaction, and was of sudden onset and short duration. As not infrequently occurs, there was a moderate neutropenia during the height of the thrombocytopenia, with absolute lymphocytosis. The bone marrow at this time showed definite evidence of damage, with destruction of the megakaryocytes and toxic changes in the megakaryoblasts, as well as stimulation of the myeloid series. These signs of damage had largely disappeared by the time of the second puncture four days later. The promptness of recovery is evidence of the transient nature of the toxic effect, and presumably dependent upon the ability of the stem cells of the marrow to produce new, active megakaryocytes. Whether the BAL contributed in any way to the favorable course it is impossible to say, as recovery is usually prompt without treatment.

No generalizations should be attempted on the basis of a single case, but it is evident that in this instance at least, peripheral destruction of the platelets or their pooling in dilated capillaries was not solely responsible for the thrombocytopenia, there being injury to the megakaryocytes as well.

SUMMARY

A case of acute thrombocytopenic purpura due to neoarsphenamine toxicity is reported, with examination of the marrow. It is concluded that the thrombocytopenia in this case was due at least in part to destruction of the megakaryocytes in the marrow.

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HYPERTHERMIA CAUSED BY PENICILLIN-HEPARIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS *

By KENNETH A. CROCKETT, M.D., and PAUL S. RHOADS, M.D., F.A.C.P.,
Chicago, Illinois

SINCE the advent of penicillin the literature contains numerous reports of cases and series of cases of subacute bacterial endocarditis successfully treated with penicillin alone or in combination with heparin. Many deleterious and even fatal results with heparin or heparin in combination with penicillin are on record. To these we wish to add a case report of excessive hyperthermia resulting from the administration of continuous intravenous penicillin to which

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From Wesley Memorial Hospital, Northwestern University Medical School.

a minimum amount of heparin had been added in order to obviate the frequent plugging of the intravenous needle. Rapidly accumulating evidence indicates that the use of heparin for any other reason in the treatment of this disease is useless, in fact contraindicated.

CASE REPORT

G. M., a 32 year old white male, was admitted to Wesley Memorial Hospital May 31, 1946. He had been perfectly well until January at which time he complained of malaise and developed a low grade fever. A migrating type of arthritis appeared which was accompanied by subcutaneous nodules on the dorsum of his hands and feet. A physician made the diagnosis of rheumatic fever. The arthralgia, subcutaneous nodules and fever spontaneously subsided in about three to four weeks. He felt weak, had lost 20 pounds during this episode, and did not regain his usual health. About the first of May the low grade fever reappeared. He was admitted to a hospital on May 20, because of a temperature of 104° F. plus the appearance of a tender nodule in the pulp of the thumb. Blood cultures revealed alpha hemolytic streptococci. Penicillin was started and arrangements were made for him to be transferred to Wesley Memorial Hospital. About 18 hours after the first penicillin had been given and before he came to Wesley Hospital, he awakened with a severe headache and was unable to move the left side of his body.

The past history revealed an illness diagnosed as lupus erythematosus at the age of 15 for which he was treated over a period of three years with gold therapy.

Physical Examination. A poorly nourished white male lying quietly in bed exhibiting a flushed facies, apathetic attitude and appearing acutely ill. He was slightly confused and a left facial palsy was observed. Temperature 101.4°, pulse 104, respirations 20. The head was normal. The pupils and fundi were normal. No petechiae were observed in and about the eyes or on the skin. The teeth were carious and the gums were retracted and inflamed. The neck was supple. There were a few small glands in the posterior triangles of the neck. The left chest did not expand well on deep inspiration nor did the left diaphragm move well. Otherwise the lungs were normal. The heart was enlarged slightly to the right and left, there was a diffuse apex impulse with a slight anterior thrust to the chest wall. A questionable thrill was palpable. Auscultation revealed an accentuated apical first heart sound with a loud rough systolic murmur heard throughout systole accompanied by soft mid-diastolic and presystolic murmurs. P_2 was greater than A_2 . The blood pressure was 118 mm. of mercury systolic and 70 diastolic. The abdomen revealed no tenderness or rigidity. The tip of the spleen was palpable and slightly tender. The liver and kidneys were not felt. The genitalia were normal. Rectal examination was normal. Tender nodules were felt in the web between the left thumb and index finger and in the pulp of the distal phalanx of the right thumb. The left arm and leg were flaccid. There was a paresis of the left side of the face except the frontalis. The tongue protruded to the left. The deep reflexes were slightly increased and there was a positive ankle clonus and Babinski on the left. Sensation was intact.

Laboratory. The urine contained a trace of albumin and a few erythrocytes. The blood count was 4 million erythrocytes, 12.5 gm. hemoglobin, 6300 leukocytes, with a differential count of 85 per cent neutrophils, 9 per cent lymphocytes and 6 per cent monocytes. The sedimentation rate was 44 mm. per hour (micro method). A nose and throat culture showed a few staphylococci (*albus*) in the nose and many *E. coli* in the throat. Repeated blood cultures with penicillinase were negative. The prothrombin activity was 100 per cent of normal. The blood Kahn was 3 plus while the Wassermann test was negative.

Hospital Course (figure 1). In view of the recent cerebral accident (assumed to be an embolus) and the diagnosis of subacute bacterial endocarditis at the previous hospital with the recovery of the *alpha* hemolytic streptococcus and in view of the fact that the patient had received 2 million units of penicillin during the 48 hours preceding admission it was considered unwise to discontinue penicillin until we had secured positive blood cultures and reestablished the diagnosis. Hence 1.5 million units of penicillin were dissolved in 1000 c.c. of 5 per cent glucose in distilled water and given daily by continuous intravenous drip. From the first to the eighth hospital day that dosage was maintained. By the fourth hospital day the temperature and pulse had returned to normal and remained there. On the ninth to eleventh hospital days the penicillin was reduced to 1 million units daily. Because of the difficulty experienced with the needle clogging and the scarcity of veins, on the twelfth and thirteenth hospital days the patient received 100 thousand units of penicillin intra-

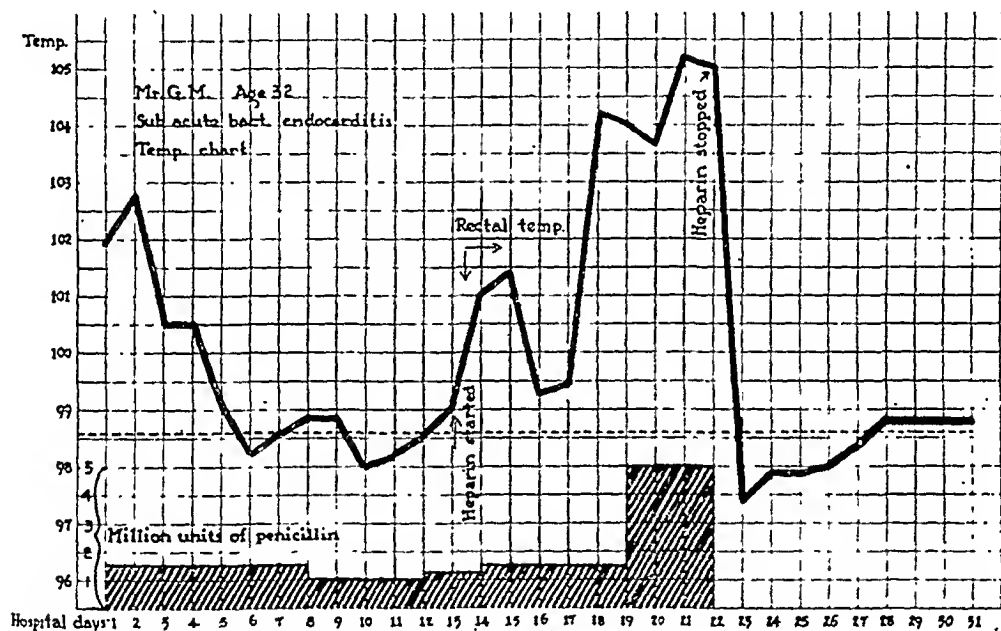


FIG. 1. Febrile course and therapy in hospital.

muscularly every two hours. Due to the patient's complaint of pain at the site of injections, penicillin was resumed by continuous intravenous drip but to each 1000 c.c. was added 20 mg. of sodium heparin to eliminate the trouble with the needle. Inasmuch as the temperature rose to 101° F. on that day and 101.4° the following day, on the sixteenth to eighteenth hospital days the penicillin dosage was increased again to 1.5 million units.

In spite of the increased dosage of penicillin, the absence of positive blood cultures, and no clinical evidence of fresh emboli the temperature gradually rose to 104.2° F. The dosage of penicillin was increased on the nineteenth hospital day to five million units and was thus maintained on the twentieth, twenty-first and twenty-second hospital days. The temperature remained between 104° and 105.2° F., occasionally falling to normal to be followed by a chill and an elevation again. The patient became clinically worse, evidence of beginning decompensation appeared, the blood non-protein nitrogen rose to 52 mg. per cent, the CO₂ combining power fell to 30 volumes per cent and the patient became gradually comatose.

By the evening of the twenty-second hospital day it appeared that unless a radical

change occurred this patient would not survive the night and since febrile reactions from heparin up to 108° F. with mental disturbances had been reported by Levy and McKrill¹ it was decided to discontinue medication. By 10 p.m. the temperature had fallen to 96° F. rectally. The patient appeared clinically improved. Orientation returned within 24 hours but the rectal temperature remained subnormal for nine days following discontinuance of therapy.

The temperature, pulse rate and blood cultures have remained normal since that time although the sedimentation rate has remained elevated. On the sixty-seventh hospital day an infected molar was removed along with the simultaneous administration of penicillin for 24 hours without untoward results. On the seventieth hospital day two additional molars were extracted while the patient was receiving a continuous intravenous infusion of penicillin and heparin for 24 hours with no reaction. On the seventy-sixth hospital day two remaining infected molars were removed accompanied by penicillin for 24 hours without incident. The patient was discharged on the seventy-ninth hospital day clinically cured although he still had an elevated sedimentation rate. He was able to walk with a circumducted gait. The paresis of the face had improved although the left arm remained useless.*

DISCUSSION

Cultures of the alpha hemolytic streptococci were obtained from the previous hospital and titrated against various antibiotics and found to be extremely resistant in vitro by the Heilmann plate method² requiring 6 units of penicillin or 8 units of streptomycin per c.c. to inhibit growth. Sulfadiazine did not inhibit growth up to 25 mg. per cent concentration. Penicillin assays revealed that the blood levels in our case varied between 0.5 and 2.0 units per c.c. and were consistent with those reported by Dawson and Hunter³ and Avery, Mayer and Nelson⁴ for similar dosage. The sodium heparin in the dosage used did not affect the coagulation time of the blood as measured by the Lee and White method. No sodium paraaminohippurate was available to try renal blockade of penicillin^{5,6} and we hesitated to use diodrast⁷ in the dosage required, hence the increase to 5 million units per day on the nineteenth hospital day. In spite of or because of increased medication the patient's condition became worse—his fever persisted and he appeared moribund. Within four hours from the time the medication was stopped the temperature had fallen to subnormal and the patient was clinically improved although still critically ill. For nine days the temperature remained subnormal gradually approaching the base line as his clinical condition improved.

Whether the hyperthermia was on the basis of penicillin, heparin, or a combination of the two, or whether pyrogens were liberated from the rubber tubing was undetermined. However, there was no fever for several days while the patient was receiving penicillin prior to the addition of heparin to the solution. No chemical thrombophlebitis or phlebothrombosis was encountered due to the continuous intravenous infusion, although occasionally the needle had to be started at a different site because of mild inflammation along the course of the vein.

Penicillin was used at the time of tooth extractions both alone and in combination with heparin in a similar manner to its administration during the course of the illness without untoward effect. We felt justified in this course of action

* At the time this report was proof read, January 6, 1948, approximately 17 months after discharge from the hospital there had been no recurrence of the endocarditis.

both as a precautionary measure against the transient bacteremia⁸ and also to try to establish the cause of the fever during the therapy. The same penicillin was used throughout, but unfortunately a different lot number of heparin was employed for the extractions.

We feel that this case should be added to those unusual reactions occurring during therapy of a disease which makes it extremely difficult to determine whether the unfavorable reaction of the patient is due to the disease process or to the medication.

SUMMARY

A case of subacute bacterial endocarditis with recovery is reported. Prolonged hyperthermia of alarming degree accompanied the use of large amounts of penicillin with minimal amounts of heparin. The evidence points toward heparin as the cause of the hyperthermia.

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EDITORIAL

THE PRESENT STATUS OF FOLIC ACID IN THE THERAPY OF MACROCYTIC ANEMIA

THE control of Addisonian pernicious anemia by the use of liver undoubtedly represents one of the most notable contributions of modern medicine to the welfare of mankind. Castle's hypothesis,¹ conceived as a result of a series of ingenious clinical investigations, supplied the theoretical basis for an understanding of the mode of development of this and related macrocytic anemias. The effectiveness of extracts of liver in a variety of clinical entities has usually been explained by reference to this "unitarian" hypothesis which was based upon the interaction of an "extrinsic" dietary factor with an "intrinsic" gastric factor leading to the formation of the anti-pernicious anemia principle subsequently absorbed through the intestinal wall and stored in the liver. Critical investigations carried out in an effort to challenge the hypothesis have usually been unsuccessful. Nevertheless, in the case of certain well-defined entities, for example, tropical macrocytic anemia and "pernicious" anemia of pregnancy, characterized not only by peripheral macrocytosis but by distinct megaloblastic hyperplasia of the marrow, application of the hypothesis has not been entirely successful. Cases of this variety have frequently demonstrated refractoriness to parenteral treatment with a highly concentrated liver extract while subsequently improving upon the oral administration of crude liver extracts or autolyzed yeast preparations.² Some factor other than the anti-pernicious anemia principle seemed to be the effective therapeutic agent and Castle and Watson³ proposed the use of the term "Will's Factor," named for Lucy Wills, a pioneer in the investigation of these anemias.

There has been no definite way hitherto of determining whether a single substance in liver extract was responsible for the improvement observed in the varied pathological manifestations of pernicious anemia. It has been long suspected, however, that multiple deficiencies existed in this disease. The chemical structure of the factors concerned in the Castle hypothesis has not been determined. The occurrence of the extrinsic factor in many foods which are a rich source of the vitamin B complex led early to consideration of a possible relationship. However, with the isolation and synthesis of each new member of the complex its ineffectiveness in the treatment of pernicious anemia was established.⁴

¹ CASTLE, W. B., TOWNSEND, W. C., HEATH, C. W., and STRAUSS, M. C.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia, I-IV, *Am. Jr. Med. Sci.*, 1929, clxxviii, 748, 764; 1930, clxxx, 305; 1931, clxxxii, 741.

² WILLS, L., and EVANS, B. D. F.: Tropical macrocytic anemia: its relation to pernicious anemia, *Lancet*, 1938, ii, 416.

³ WATSON, J., and CASTLE, W. B.: Nutritional macrocytic anemia especially in pregnancy. Response to a substance other than that effective in pernicious anemia, *Am. Jr. Med. Sci.*, 1946, ccxi, 513.

⁴ CASTLE, W. B., ROSS, J. B., DAVIDSON, C. S., BURCHENAL, J. H., FOX, H. J., and HAM, T. H.: Extrinsic factor in pernicious anemia: ineffectiveness of purified casein and of identified components of the vitamin B complex, *Science*, 1944, c, 81.

The recent isolation and synthesis of "folic" acid has for the first time furnished a pure substance which could apparently produce a hematologic and clinical remission in Addisonian anemia. Folic acid was found to be equally effective whether given parenterally or orally. Its effectiveness on oral administration immediately challenged its identification with extrinsic factor. Further difficulty was encountered when identification with the anti-pernicious anemia principle of concentrated liver extract was attempted. It was found ⁵ that commercial liver extracts highly effective in treatment contained only infinitesimal quantities of folic acid, far below the therapeutic requirement for the pure vitamin. The relationship of folic acid to the factors concerned in the Castle hypothesis is interesting to examine in more detail.

The isolation ⁶ and synthesis ⁷ of folic acid represented the culmination and integration of many apparently divergent paths of investigation. A central purpose of these efforts had been attempts to determine the nutritional requirements of bacteria and animals. It is perhaps now more of historical interest than anything else to mention some of the factors determined in these nutritional studies which have since been identified with folic acid. Some of the more completely studied ones may be briefly mentioned. Day et al.⁸ described a deficiency state of monkeys characterized by weight loss, diarrhea, gingivitis, anemia, leukopenia and thrombocytopenia which could be corrected by some substance present in yeast and liver to which the term vitamin M was applied. Hogan and Parrott⁹ presented evidence for the existence of an unidentified factor necessary, in addition to the known vitamins for the prevention of anemia in chicks. A factor in liver designated vitamin B_c was found to prevent the development of this anemia. Snell and Peterson¹⁰ reported that *Lactobacillus casei* grown in synthetic medium required the addition of a norite eluate factor, derived from yeast or liver, for maximal growth. Mitchell, Snell and Williams¹¹ were the first to use the term "folic acid" in referring to a substance derived from spinach and required for maximal growth of *Streptococcus lactis* R. The latter term, folic acid, has, in common parlance, "stuck." One could continue to enumerate additional similar paths of investigation. Suffice it to say that in 1941,

⁵ CLARK, G. W.: Vitamin content of liver extracts for parenteral use, Am. Jr. Med. Sci., 1945, ccix, 520.

⁶ PFIFFNER, J. J., BINKLEY, S. B., BLOOM, E. S., BROWN, R. A., BIRD, O. D., EMMETT, A. D., HOGAN, A. G., and O'DELL, B. L.: Isolation of the anti-anemia factor (vitamin B_c) in crystalline form from liver, Science, 1943, xcvi, 404.

⁷ ANGIER, R. B., BOOTHE, J. H., HUTCHINGS, B. L., NOWAT, J. H., SEMB, J., STOKSTAD, E. L. R., SUBBAROW, Y., WALLER, C. W., COSULICH, D. B., FAHRENBACH, M. J., HULTQUIST, M. E., KUH, E., NORTHEY, E. H., SEEGER, D. R., SICKELS, J. P., and SMITH, J. M., JR.: Synthesis of a compound identical with the *L. casei* factor isolated from liver, Science, 1945, cii, 227.

⁸ DAY, P. L., LANGSTON, W. C., and DARBY, W. J.: Failure of nicotinic acid to prevent nutritional cytopenia in the monkey, Proc. Soc. Exper. Biol. and Med., 1938, xxxviii, 360.

⁹ HOGAN, A. G., and PARROTT, E. M.: Anemia in chicks caused by a vitamin deficiency, Jr. Biol. Chem., 1940, cxxxii, 507.

¹⁰ SNELL, E. E., and PETERSON, W. H.: Growth factors for bacteria. X. Additional factors required by certain lactic acid bacteria, Jr. Bact., 1940, xxxix, 273.

¹¹ MICHELL, H. K., SNELL, E. E., and WILLIAMS, R. J.: The concentration of "folic acid," Jr. Am. Chem. Soc., 1941, lxiii, 2284.

Hutchings et al.¹² suggested a similarity between the chick vitamins and the bacterial growth factors; and that in 1943 the *L. casei* factor⁶ was isolated in crystalline form from liver and was synthesized in 1945.⁷ It proved to be a relatively simple organic compound containing the amino acid, glutamic acid, para-aminobenzoic acid and the pterin nucleus. To this compound the chemical term pteroylglutamic acid (PGA) was applied. Popular usage, however, has led to the persistence of the term folic acid which is used synonymously with pteroylglutamic acid.

A series of compounds apparently exists in nature similar to pteroylglutamic acid but differing often from each other solely in regard to the number of glutamic acid molecules which they contain. The commonest form in which the vitamin occurs in food appears to be a compound containing seven molecules of glutamic acid, pteroylhepta glutamic acid.¹³ Microbiological assays with *L. casei* and *S. lactis R* indicate that the conjugated vitamin is relatively impotent in stimulating the growth of these organisms in marked contrast with the mono-glutamic acid form.¹⁴ Hydrolysis of the conjugate with release of PGA results in optimal growth. In humans, administration of the conjugate to normal individuals results in the excretion of pteroylglutamic acid.¹⁵ The existence of an enzyme, vitamin B₉ conjugase, or more simply conjugase, was postulated and found to occur in abundant amounts in liver, kidney, bone marrow and pancreas.¹⁸ An additional factor to be taken into consideration in this relationship was the demonstration by Bird et al.¹⁶ of the presence in yeast extracts, and probably other foods, of a strong inhibitor of conjugase.

On the basis of available data, it would appear that pteroylglutamic acid occurring usually in conjugated form and accompanied by variable amounts of conjugase inhibitor, is hydrolyzed in the body by the enzyme, conjugase, and thereby liberated for use in metabolic processes chiefly concerned with hematopoiesis but possibly with other body activities. The optimal daily allowance of this nutrient has not yet been determined, nor has the exact mode of its action been ascertained. Several possibilities have been suggested. It has been observed that thymine, a pyrimidine base occurring in nucleoproteins, can be substituted for PGA in the maintenance of optimal growth of *S. lactis R*. Spies and coworkers¹⁷ have reported the successful

¹² HUTCHINGS, B. L., BOHONOS, N., and PETERSON, W. H.: Growth factors for bacteria. Purification and properties of an eluate factor required by certain lactic acid bacteria, Jr. Biol. Chem., 1941, cxli, 521.

¹³ OLSON, O. E., BURRIS, R. H., and ELVEHJEM, C. A.: Preliminary report of folic acid content of certain foods, Jr. Am. Diet. Assoc., 1947, xxiii, 200.

¹⁴ JUKES, T. H.: Pteroylglutamic acid in nutrition, Jr. Am. Diet. Assoc., 1947, xxiii, 193.

¹⁵ SWANSEID, M. E., BIRD, O. D., BROWN, R. A., and BETHELL, F. H.: Metabolic function of pteroylglutamic acid and its hexaglutamyl conjugate. II. Urinary excretion studies on normal persons. Effect of a conjugase inhibitor, Jr. Lab. and Clin. Med., 1947, xxxii, 23.

¹⁶ BIRD, O. D., ROBBINS, M., VAN DEN BELT, J. M., and PFIFFNER, J. J.: Observations on vitamin B₉ conjugase from hog kidney, Jr. Biol. Chem., 1946, clxiii, 649.

¹⁷ SPIES, T. D., FROMMEYER, W. B., JR., VILTER, C. F., and ENGLISH, A.: Anti-anemic properties of thymine, Blood, 1946, i, 185.

substitution of thymine in large amounts for folic acid in the treatment of several patients with macrocytic anemia. These investigators suggest that folic acid, like other members of the B complex, acts as a co-enzyme in the synthesis of thymine. The studies of Daft¹⁸ suggest that folic acid may play a rôle in nitrogen metabolism.

Recent studies by Bethell et al.,^{15, 19} utilizing both free folic acid and the heptaglutamic acid conjugate, shed some light upon the possible physiologic defect in pernicious anemia and related macrocytic anemias. Investigations were made upon a group of patients which included nine pernicious anemias in relapse, two post-gastrectomy macrocytic anemias, and one case each of cirrhosis of the liver and possible non-tropical sprue. In addition, three pernicious anemia patients in remission and seven normal individuals were studied. When pteroylheptaglutamic acid is given orally without conjugase inhibitor to the normal subject, urinary excretion levels for pteroylglutamic acid parallel those obtained after administration of the pure vitamin. The simultaneous administration of conjugase inhibitor and pteroylheptaglutamic acid resulted in lower PGA excretion levels in these persons. The pernicious anemia patients in relapse were studied both in regard to their hematopoietic response and urinary excretion of PGA during the administration of pteroylheptaglutamic acid. When the latter was administered in association with large amounts of conjugase inhibitor, the hematopoietic response was poor and the urinary levels of PGA were low. On the other hand, when the pteroylheptaglutamic acid was administered with lesser amounts of conjugase inhibitor a definite hematopoietic response ensued. Synthetic folic acid administered to these patients likewise resulted in satisfactory hematopoietic responses. Folic acid conjugate was also administered to pernicious anemia patients in remission resulting in the urinary excretion of PGA in amounts approximately equal to those obtained in normal subjects. It was concluded, therefore, that in patients with pernicious anemia there exists an inability to neutralize conjugase inhibitor usually present in most foods containing folic acid conjugate and that as a result a deficiency of folic acid occurs. It was further suggested that one of the pharmacologic actions of liver may be the correction of the metabolic defect in the utilization of naturally-occurring conjugated form of pteroylglutamic acid.

These observations have not yet been repeated and confirmed. Bethell et al. point to the occasional failure of PGA to induce and maintain complete hematopoietic remissions in some pernicious anemia patients; and to the additional important observation that the progression of neurologic disturbances in some individuals is not halted. These facts suggest that the action of liver extract may be more complex than simply to relieve a conditioned nutritional

¹⁸ DAFT, F. S.: Folic acid. Physiological aspects, *Ann. N. Y. Acad. Sci.*, 1946, xlviii, 299.

¹⁹ BETHELL, F. H., MEYERS, M. C., ANDREWS, G. A., SWANSEID, M. E., BIRD, O. D., and BROWN, R. A.: Metabolic function of pteroylglutamic acid and its hexaglutamyl conjugate. I. Hematologic and urinary excretion studies on patients with macrocytic anemia, *Jr. Lab. and Clin. Med.*, 1947, xxxii, 3.

deficiency of folic acid. There are now in the literature a number of reports^{20, 21, 22} dealing not only with the failure of folic acid to prevent the progression of neurologic disturbances present at the onset of treatment, but with the observation that neurologic disorders of a rapidly progressive type may actually develop during the course of folic acid therapy. Increasing the daily dose of the vitamin to as much as 500 mg. per day did not result in a beneficial effect on the nervous system lesions.²⁰ Furthermore a rather high incidence of persistent glossitis in folic acid treated patients has also been observed.

There can be no doubt concerning the fundamental biological importance of folic acid in human, animal and bacterial metabolism. In pernicious anemia, folic acid deficiency induced by an inability to utilize the naturally-occurring vitamin conjugate may be an important factor in the production of the anemia. That this is not the only physiologic disturbance in Addisonian anemia is well known. Until the time when all separate manifestations of the disease can be controlled by specific synthetic substances, the use of concentrated liver extracts must continue to be recommended for the treatment of pernicious anemia.

M. S. S.

²⁰ SPIES, T. D., and STONE, R. D.: Liver extract, folic acid, and thymine in pernicious anemia and subacute combined degeneration, *Lancet*, 1947, i, 174.

²¹ HEINLE, R. W., and WELCH, A. D.: Folic acid in pernicious anemia: failure to prevent neurologic relapse, *Jr. Am. Med. Assoc.*, 1947, cxxxiii, 739.

²² WAGLEY, P. F.: Neurologic disturbances with folic acid therapy, *New Eng. Jr. Med.*, 1948, ccxxxviii, 11.

REVIEWS

Neutron Effects on Animals. By the Staff of the Biochemical Research Foundation, Dr. Ellice McDonald, Dir. vii + 198 pages; 23.5 × 16 cm. Williams and Wilkins Company, Baltimore. 1947. Price, \$3.00.

This book is essentially a collection of papers by a group of investigators attempting to evaluate the biological action and potentialities of neutrons. The first chapter by McDonald outlines the scope and purpose of the project. It points out that when atomic energy is applied industrially, one of the problems will be the protection of workers against the chief by-product "neutron bombardment." For those who wish to refresh their memories and perhaps modernize their concept of the various types of electromagnetic and subatomic-particulate radiation, chapter two is highly recommended.

Chapter three describes the technic involved in the production of neutrons and the exposure of animals to these. The chapters which follow describe the specific effects of neutrons on rats, rabbits, dogs, and various bacteria and other micro-organisms. The method of measuring the dosages is somewhat similar to that for measurement of x-rays in that Victoreen ionization chambers are used to measure radiation intensity. The units are expressed, however, as neutron radiation intensity, abbreviated as "n" to distinguish this unit from the roentgen. In these and other studies the biological effect of an n-unit of neutrons is different from that of an r-unit of x-rays even though both give the same reading when measured with a Victoreen 100-r chamber.

In rats the medium lethal dose for neutrons lay between 60-n and 120-n. Neutron doses above 180-n caused death of rats in from six to eight days accompanied by extreme loss of weight and maximum leukopenia. A high percentage of the rats surviving for more than 150 days developed malignant tumors of various types. Attention was called to the fact that no ovarian tumors were observed in the neutron treated rats whereas Furth has reported a consistent induction of ovarian tumors in mice with 50-r of x-radiation. The authors raise the question of whether or not this indicates a difference between the action of x-rays and neutrons. In the reviewer's opinion this would appear to be a matter of differences in the time of observation. Furth's animals developed ovarian tumors approximately one year after radiation. The data given for the rats in this book do not appear to extend over more than 150 days.

Numerous other specific effects of neutrons are described and in general, testicular changes, blood changes, and other physiological effects were similar to those which follow treatment with x-rays and gamma radiation. Since the gamma radiation was screened out by three inches of lead, these effects could not have been due to radiation of this type. The authors seem to have been impressed, however, by the fact that neutrons have a greater biological effect than gamma and x-radiation.

As admitted in the preface, this book has barely scratched the surface as far as future developments are concerned. The separate contributions which make up this volume are too specific for the book ever to become valuable as an elementary reference in this field, but they should serve to stimulate future work along lines that will undoubtedly assume greater importance in medical diagnostic and therapeutic procedures.

F. H. J. F.

Paravertebral Block (in Diagnosis, Prognosis, and Therapy: Minor Sympathetic Surgery). By FELIX MANDL, M.D., F.I.C.S., Professor of Surgery, Hadassah University Hospital, Jerusalem. Translated by GERTRUDE KALLNER, M.D. Foreword by MAX THOREK, M.D., F.I.C.S., Professor of Surgery, Cook County Graduate School of Medicine, Chicago. 330 pages; 23.5 × 15.5 cm. Grune and Stratton, New York. 1947. Price, \$6.50.

This is an excellent monograph dealing with paravertebral block, both as a therapeutic measure and as a method of differential diagnosis. The author discusses the anatomy and physiology of the sympathetic system, and their relationship to the technic of paravertebral injections. Numerous case histories are cited, with an analysis of both satisfactory and unsatisfactory results. The results of paravertebral block are discussed and compared with those of other methods. To all physicians interested in paravertebral block this book will serve as an excellent reference.

G. H. Y.

Peripheral Vascular Diseases (Angiology). 2d Ed. By SAUL S. SAMUELS, A.M., M.D., Consulting Vascular Surgeon, Long Beach Hospital, Long Beach, New York; Attending Vascular Surgeon, Brooklyn Hospital for the Aged; Chief of the Department of Peripheral Arterial Diseases, Stuyvesant Polyclinic Hospital, New York; Fellow in Surgery, New York Academy of Medicine; Member of Committee on Surgery, New York Diabetes Association. 85 pages; 22 × 14 cm. Oxford University Press, London, New York, Toronto. 1947. Price, \$2.50.

This is a concise outline of peripheral vascular diseases, that also includes outlines of the anatomy of the vascular system and of the autonomic nervous system. A concise classification of peripheral vascular disease is given with an excellent résumé of the symptomatology of peripheral arterial disease and of the objective signs of arterial occlusion. Each disease entity is individually and briefly outlined, and valuable therapeutic suggestions are given.

G. H. Y.

The Selected Writings of Benjamin Rush. Edited by DAGOBERT D. RUNES. 433 pages; 21 × 14 cm. Philosophical Library, New York City. 1947. Price, \$5.00.

To those physicians interested in medical history and to those who particularly admire the writings of Benjamin Rush, this volume will be a source of enjoyment and one which will find a welcome place in their private libraries.

These selected writings of Benjamin Rush serve to emphasize his profound learning and his skill in observation. They indicate also the breadth of his interests which extended beyond his classic contributions to the field of medicine to such fields as government, education, religion and natural history. One gains in reading this book a deeper insight into the mind and culture of this great physician and champion of the American Revolution.

The frontispiece is a reproduction of the fine engraving of Benjamin Rush by William Haines. The appendix contains a list of writings published during his lifetime and a selected bibliography. There is an adequate index.

J. E. S.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

- American Medical Research, Past and Present.* By RICHARD H. SHRYOCK, Ph.D., Professor of History and Lecturer in Medical History, University of Pennsylvania, etc. 350 pages; 21.5 × 14 cm. 1947. The Commonwealth Fund, New York. Price, \$2.50.
- American Pharmacy: Advanced Pharmacy—Medical, Surgical and Dental Supplies—Animal Health Pharmacy* (Vol. II). Editor-in-Chief: RUFUS A. LYMAN, M.D., Director, School of Pharmacy, University of Arizona. 379 pages; 26 × 18.5 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, \$7.00.
- Congenital Malformations of the Heart.* By HELEN B. TAUSSIG, M.D., Associate Professor of Pediatrics, Johns Hopkins University School of Medicine, etc. 618 pages; 26 × 18 cm. 1947. The Commonwealth Fund, New York. Price, \$10.00.
- The Contemporary American Family.* By ERNEST R. GROVES and GLADYS HOAGLAND GROVES. 838 pages; 22.5 × 15 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, \$4.50.
- 400 Years of a Doctor's Life.* Collected and arranged by GEORGE ROSEN, M.D., and BEATE CASPARI-ROSEN, M.D. 429 pages; 23.5 × 16 cm. 1947. Henry Schuman, New York. Price, \$5.00.
- Gynecological and Obstetrical Urology* (2d Ed.). By HOUSTON S. EVERETT, A.B., A.M., M.D., Associate Professor of Gynecology, The Johns Hopkins University, etc. 539 pages; 24 × 16 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, \$6.00.
- Hormones and Behavior: A Survey of Interrelationships Between Endocrine Secretions and Patterns of Overt Response.* By FRANK A. BEACH, Professor of Psychology, Yale University; with a Foreword by EARL T. ENGLE. 368 pages; 24 × 16 cm. 1948. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$6.50.
- The Parathyroid Glands and Skeleton in Renal Disease.* By J. R. GILMOUR, M.R.C.P., Pathologist in Emergency Medical Service, Junior Assistant Director, Bernhard Baron Institute of Pathology, London Hospital. 157 pages; 22 × 14 cm. 1947. Oxford University Press, New York. Price, \$5.75.
- Practical Office Gynecology.* By KARL JOHN KARNAKY, M.D., Assistant Professor of Clinical Gynecology, Baylor University College of Medicine, etc. 261 pages; 26 × 18 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, \$7.50.
- Radium Dosage: The Manchester System.* Compiled from Articles by RALSTON PATERSON, F. W. SPIERS, S. K. STEPHENSON, H. M. PARKER, M. C. TOD, and W. J. MEREDITH. Edited by W. J. MEREDITH, M.Sc., F.Inst.P., Christie Hospital and Holt Radium Institute, Manchester. 124 pages; 26 × 19 cm. 1947. The Williams and Wilkins Company, Baltimore. Price, \$4.50.
- Teaching Psychotherapeutic Medicine: An Experimental Course for General Physicians.* Edited by HELEN LELAND WITMER, Ph.D.; Introductory Chapter by GEDDES SMITH. 464 pages; 24 × 16 cm. 1947. The Commonwealth Fund, New York. Price, \$3.75.

COLLEGE NEWS NOTES

ADDITIONAL LIFE MEMBERS

The American College of Physicians takes especial pride in announcing the addition to the Roster of Life Members of the College of the following Fellows, as of the dates given.

Maurice Kovnat, Miami Beach, Fla., December 15, 1947
Edgar Wayburn, San Francisco, Calif., December 22, 1947
Ross Paull, La Jolla, Calif., December 26, 1947
Lawrence E. Geeslin, Jacksonville, Fla., December 29, 1947
George Baehr, New York, N. Y., January 3, 1948
Worth B. Daniels, Washington, D. C., January 3, 1948
S. Douglas Craig, Winston-Salem, N. C., January 5, 1948
Leon Bromberg, St. Louis, Mo., January 5, 1948
Frederic T. Billings, Jr., Nashville, Tenn., January 9, 1948
Herman A. Dickel, Portland, Ore., January 9, 1948
Leon S. Lippincott, Daytona Beach, Fla., January 10, 1948
Marsh McCall, New York, N. Y., January 10, 1948
Joseph F. McVeigh, Fort Worth, Tex., January 10, 1948
Donald E. Forster, Portland, Ore., January 12, 1948
I. S. Kahn, San Antonio, Tex., January 12, 1948
Carl S. Leede, Seattle, Wash., January 12, 1948
Carlyle Morris, Metuchen, N. J., January 12, 1948
F. Sullivan Hassett, Elmira, N. Y., January 13, 1948
Edward Weiss, Philadelphia, Pa., January 13, 1948
Charles C. Wolferth, Philadelphia, Pa., January 13, 1948

NOTICE OF PROPOSED AMENDMENT TO THE CONSTITUTION OF THE AMERICAN COLLEGE OF PHYSICIANS

The By-Laws of the College were amended at the 1947 Annual Session of the College, and, among other things, provided a new Article VI for the election of Masters, in which it is specified, "a special Committee on Masterships will be named by the President. This Committee will consist of two members from the Board of Regents and one member from the Board of Governors. It will bring in nominations of Master to the Board of Regents for election or rejection."

That amendment makes it necessary for an amendment to the Constitution, Article IV, (b), substituting in line 5, "Committee on Mastership" in the place of "Committee on Credentials." Namely; this paragraph shall be amended to read:

"Masters of the American College of Physicians shall be those who have attained the rank of Fellows, and who on account of personal character, positions or influence and honor, eminence in practice or in medical research, or other attainments in science or in the art of medicine, are recommended by the Committee on Masterships to the Board of Regents for special and well-earned distinction. Such Masters shall be designated as Masters of the American College of Physicians, and shall be authorized to use the letters M. A. C. P. in connection with scientific publications, at professional and academic functions and in connection with their professional activities."

This amendment shall be submitted to the members at the next annual business meeting at San Francisco, April 22, 1948, for approval.

AMERICAN TRUDEAU SOCIETY ANNOUNCES COURSES IN THORACIC DISEASES

The American Trudeau Society announces the following postgraduate courses in thoracic diseases:

March 22-26, 1948—Herman Kiefer Hospital, Detroit, Mich. (Detroit Department of Health and Wayne University College of Medicine cooperating); Chairman, Dr. Paul T. Chapman, Herman Kiefer Hospital; fee, \$50.00.

March 22-27, 1948—North Carolina Sanatorium, Sanatorium, N. C. (Medical Schools of University of North Carolina and Duke University cooperating); Chairman, Dr. Henry Stuart Willis, North Carolina Sanatorium; fee, \$50.00.

April 5-17, 1948—Boston, Mass. (Medical Schools of Harvard, Tufts and Boston Universities cooperating); Chairman, Dr. Theodore L. Badger, 264 Beacon St., Boston, Mass.; fee, \$100.00.

April 12-24, 1948—Plans not yet completed but course will be held at Dallas, Tex.; Chairman, Dr. Julius L. Wilson, 1430 Tulane Ave., New Orleans 13, La.; fee, \$100.00.

POSTGRADUATE ASSEMBLY IN ENDOCRINOLOGY

The Association for the Study of Internal Secretions announces through Dr. E. Kost Shelton, F.A.C.P., Chairman of the Committee on Postgraduate Instruction, a Postgraduate Assembly in Endocrinology at Los Angeles, February 23-28, 1948. Many outstanding students of endocrinology in the United States and Canada appear on the faculty. Applications should be filed with Dr. Shelton at 921 Westwood Boulevard, Los Angeles 24, Calif.

AMERICAN COLLEGE OF RADIOLOGY OFFERS TWO POSTGRADUATE COURSES

The American College of Radiology will offer courses in radiology at Philadelphia, February 2-6, 1948, under the joint sponsorship of the College and the Philadelphia Roentgen Ray Society, and at Chicago, March 8-12, 1948, in collaboration with the Chicago Roentgen Society. Fee will be \$50.00 for each course. Details are available through the American College of Radiology, 20 N. Wacker Drive, Chicago 6, Ill.

The Interamerican Society of Cardiology has authorized the meeting of the III Interamerican Cardiological Congress, to be held in Chicago, Illinois, at the Michael Reese Hospital, from June 13 to June 17, 1948. This meeting will take place immediately before the American Heart Association annual meeting, June 18 and 19, and the American Medical Association meeting the week of June 20. Inquiries regarding the Congress may be addressed to the offices of the III Interamerican Cardiological Congress, at the Michael Reese Hospital, Chicago, Illinois.

Cornell University Medical College celebrates its Fiftieth Anniversary this year. The Alumni Day will be held on March 11 at the College, and is of special significance to all of our alumni. The program will include registration in the morning, with luncheon at the Nurses Residence, to be followed by the business meeting and a schedule of rounds and conferences in all departments. Dinner will be served at the Roosevelt Hotel and dancing will conclude the day.

DR. ARDEN FREER SUCCEEDS DR. PAUL R. HAWLEY AS COLLEGE GOVERNOR
FOR THE VETERANS ADMINISTRATION

Due to the resignation of Dr. Paul R. Hawley, Chief Medical Director of the Veterans Administration and also as the College Governor for the Veterans Administration, the Deputy Medical Director, Dr. Arden Freer, F.A.C.P., has been appointed by President Hugh J. Morgan of the College as Governor for the Veterans Administration until the next regular election. Effective January 1, 1948.

It was recently announced that Dr. Hawley will undertake on April 1, 1948, the position of Chief Executive Officer of the Blue Cross and Blue Shield health service plans. Dr. Hawley's offices will be in Chicago.

Grateful acknowledgment is made of the kindness of Herbert T. Kelly, M.D., F.A.C.P., Philadelphia, Pa., for his contribution to the College Library of Publications by Members of a copy of the new 5th edition of "Simplified Diabetic Management," by Joseph T. Beardwood, Jr., M.D., F.A.C.P., and Dr. Kelly. This book was published by the J. B. Lippincott Company, Philadelphia.

Dr. Joseph T. Roberts, F.A.C.P., formerly Chief Medical Officer in the Department of Medicine, Gallinger Municipal Hospital, Washington, D. C., has been appointed Dean of the University of Arkansas School of Medicine at Little Rock, having assumed his duties there during the autumn of 1947.

NEWS FROM PUERTO RICO

Luis M. Morales, San Juan, Puerto Rico, has been elected a member of the Council of the National Committee for Mental Hygiene.

The following Fellows of the College were among the speakers of the 44th Annual Meeting of the Medical Society of Puerto Rico, which was held at San Juan, December 10-14, 1947: Drs. Richard A. Kern and William D. Stroud, Philadelphia; Dr. Cecil J. Watson, Minneapolis, Minn.; Dr. Charles F. McKhann, Cleveland, Ohio; Dr. Louis Krause, Baltimore, Md.; Dr. Solomon Katzenelbogen, Washington, D. C.; and Drs. Roberto Francisco Azize, Rurico S. Diaz-Rivera, Federico Hernandez-Morales, Ramón M. Suárez, and Enrique Koppisch, all of San Juan. The Chairman of the program Committee was the College Governor for Puerto Rico, Dr. Suárez.

ABRIDGED MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

NOVEMBER 23, 1947

THE regular autumn meeting of the Board of Regents was held at the College Headquarters, Philadelphia, Pa., beginning at 9:50 a.m., November 23, 1947, with President Hugh J. Morgan presiding, and the following in attendance:

Hugh J. Morgan	<i>President</i>
Walter W. Palmer	<i>President-Elect</i>
Reginald Fitz	<i>First Vice President</i>
Francis G. Blake	<i>Second Vice President</i>
William D. Stroud	<i>Treasurer</i>
George Morris Piersol	<i>Secretary-General</i>
Walter B. Martin	
William S. Middleton	
James E. Paullin	
LeRoy H. Sloan	
Ernest E. Irons	
William S. McCann	
T. Grier Miller	
Charles F. Moffatt	
Charles F. Tenney	
David P. Barr	
A. B. Brower	
Alex. M. Burgess	
Ernest H. Falconer	
Cyrus C. Sturgis	
Maurice C. Pincoffs	<i>Editor, ANNALS OF INTERNAL MEDICINE</i>
Walter L. Palmer	<i>Chairman, Board of Governors</i>
Edward L. Bortz	<i>Chairman, Advisory Committee on Postgraduate Courses</i>
William J. Kerr	<i>Chairman, 29th Annual Session</i>
Edward R. Loveland	<i>Secretary, Board of Regents</i>

The Secretary, Mr. E. R. Loveland, read abstracted Minutes of the preceding meetings, which upon motion were approved as read.

Among the more important communications presented by the Secretary were the following:

A cablegram from the Royal Australasian College of Physicians, informing the College that President Hugh J. Morgan had been unanimously elected an Honorary Fellow of that College;

Notice from the Gorgas Memorial Institute of Tropical and Preventive Medicine, advising of the election of President Hugh J. Morgan to the Board of Directors of that institution;

A notice from the Executive Committee of approval of the reassignment of the Governors' territorial areas of Eastern and Western New York, the new division providing that Western New York be enlarged to include all of Northern New York and East to Albany, then extending diagonally Southwest to Binghamton and then directly South to the Pennsylvania border;

A report on the approval by the Executive Committee, through President Morgan, of the Medical Library Association's project to provide adequate abstracting and indexing of medical literature;

A recommendation from Dr. George F. Strong, Regent, that the Provinces of Manitoba and Saskatchewan be separated from the present area, which includes also Alberta and British Columbia, and that a separate Governor be elected to represent Manitoba and Saskatchewan. (The Board of Regents approved the recommendation by formal resolution.) ;

A reminder that the American College of Physicians a year ago agreed to participate in the Fourth International Congress on Tropical Medicine and Malaria, sponsored through the State Department and to be held in this country in 1948, with the subsequent appointment of Dr. Joseph M. Hayman, Jr., of Cleveland, as the official representative of the College. Said Congress will be held in Washington, May 10-19, 1948, and by formal resolution, the Regents voted to defray such traveling expenses as Dr. Hayman may have in connection with this appointment ;

Report of the approval by the Executive Committee of an increase, amounting to about 8 per cent, in the printing costs of the ANNALS OF INTERNAL MEDICINE as of August 1, 1947, said action being formally approved by the Board of Regents ;

A notice from Dr. William S. McCann, F.A.C.P., Chairman of the American Board of Internal Medicine, of his intention to resign from that Board as of June 30, 1948, requiring a new appointment by the College to fill out his unexpired term.

Dr. George Morris Piersol, Secretary-General, reported the deaths of two Masters and 37 Fellows since the preceding meeting of the Board, said names being spread upon the Minutes ; also the addition of 18 Fellows as Life Members, whose names also were spread upon the Minutes.

President Morgan pointed out that among those who had died were two past Presidents, Doctors Ernest B. Bradley and John H. Musser, and one former Governor, Dr. Fred W. Wilkerson. He requested Doctors James E. Paullin and David P. Barr to prepare an appropriate memorial on Dr. Ernest B. Bradley, to appear in the ANNALS, to be spread on the Minutes and to be sent to Dr. Bradley's family ; Doctors William S. Middleton and T. Grier Miller to prepare the memorial on Dr. John H. Musser ; and Doctors Walter L. Palmer and Walter B. Martin to prepare a memorial on Dr. Fred W. Wilkerson.

Dr. Piersol, as Chairman of a Committee of three, suggested the following legend for the diploma for the Alfred Stengel Memorial Award, and suggested that it be engrossed each year, because it would be impractical to have a diploma which could be struck off in quantity, since this award will be given as a very special honor from time to time and should be individualized in each instance to meet the particular occasion.

THE AMERICAN COLLEGE OF PHYSICIANS

THE ALFRED STENGEL MEMORIAL AWARD

This Award, made available through the generosity of James D. Bruce, a former Regent and President of the College, is awarded by the Regents of the American College of Physicians to

_____ M.D., F.A.C.P.
in recognition of his many years of loyal and devoted service to the College
and _____
Conferred at _____ on _____

President

Secretary-General

The Board of Regents formally approved the proposal and copy by resolution.

Dr. Ernest E. Irons, reporting for a special Committee appointed by the President, including also Doctors George H. Lathrope, J. Edwin Wood, Jr., Reginald Fitz and Edward L. Bortz, to present nominations for the Alfred Stengel Memorial Award, submitted five nominations, which were voted upon by secret ballot. The nominee (whose name may not be announced until the next annual Convocation) was unanimously selected.

At this point members of the Board of Regents personally, through Dr. James E. Paullin, presented to Miss Pearl M. Ott a beautiful Hamilton wrist watch, with appropriate engraving on the reverse side, in recognition of her twenty-first anniversary of service to the College and of the affection of the Officers and Regents.

Mr. E. R. Loveland, the Executive Secretary, presented his annual fall report, dealing with the 25 Regional Meetings conducted during the autumn, Postgraduate Courses and other administrative activities. He asked for direction from the Board with regard to the publication of a new and revised Directory of the College, or a new Membership Roster, during 1948. Due primarily to the excessive cost and shortage of paper, the Board of Regents by resolution voted to publish a Membership Roster instead of a full Directory, but to include therein the Constitution and By-Laws and other necessary announcements concerning Fellowships, Awards and other activities of import to members.

Report, American Board of Internal Medicine—Dr. William S. McCann, Chairman: Mr. President and members of the Board of Regents, the Board has chiefly to report a lot of perplexities and problems concerning which it desires more light. The American Board of Internal Medicine, in common with other specialty boards, has long prescribed the program of training to be followed for admission to its examination. In order to accomplish this, it is necessary to set some mark of approval on the hospitals at which a candidate may expect to get his necessary training. Since the War, the task of examining training facilities has become so onerous that the machinery for doing this has almost broken down, due to the large number of veterans who are seeking certification and the host of new hospitals that have set up residency training programs and are seeking approval. The Council on Medical Education and Hospitals of the American Medical Association has been the agency in the past which has accumulated the data and inspected the facilities. Its surveys, when completed, are submitted to the Board for acceptance, but even with the large facilities of the American Medical Association, the task has lagged behind and the American Board is bedeviled with complaints about delays and things of that sort. There are complaints from another angle, from the Deans and Faculties of schools who generally protest that our rather rigid requirements are setting a strait-jacket on medical education. They say the young men are forming a line and proceeding in lock step toward the goal of certification, and that they no longer enter educational institutions to learn anything. They simply want to be certified.

The American Board of Internal Medicine is acutely conscious of the justice of many of the complaints, and it has endeavored to liberalize its requirements. A plan was drawn up, which you probably have all seen. It was published in the Journal of the American Medical Association and in the ANNALS OF INTERNAL MEDICINE within the past year. Some members of the Board, who felt that the liberalization and the diversification and means of getting training were good, feel they do not go far enough, and at our last meeting we had a serious debate on the subject of doing away with the whole business of approval of training agencies and simply going back to certain basic requirements which a candidate would have to meet in order to be examined—his professional qualifications, licensure and a certain period of time following graduation. That sort of move would throw the burden of responsibility onto the candidate himself to decide where he could get adequate preparation for the examina-

tion, and I suppose in a way it could be defended, because the superior man certainly can judge the quality of the training that he gets. The inferior man may not do so, but we are not so much interested in him. The Board in that case would become purely an examining body.

There was a sharp division in the Board, and it became obvious that we could not take any drastic action of this kind, but if we are to continue some sort of supervision of the training program, it is obvious that it has got to be put into the hands of somebody of comparable jurisdiction that can provide inspection and has the personnel and facilities for carrying on inspection and scrutiny of the training agencies.

It is certainly true that that task is too great for the American Board of Internal Medicine to perform. All that we know about these agencies is what we get on paper, summarized for us by the Council, and, in view of the volume of work which has fallen on the Council, it has been impossible for them to keep abreast of the needs. If I could offer a suggestion, I would say that I think whatever body undertakes it might well be a joint creature of the College, the American Medical Association and the Association of American Medical Colleges. I believe if the latter body were included in the formation of the approving machinery, it would dispose of the problem which we now have of meeting the educational ideas of Deans and Faculties of the schools. Certainly they are entitled to their ideas and to consideration.

I think I can say that the Association of American Medical Colleges is going into a new phase. It has increased its income by raising the dues to the member Colleges, and it is going to cut down the expenditures of money on publishing a magazine; it is due to get a new Director or Secretary, who can be chosen for his vigor and youthful enthusiasm, and it is possible that this body could be made to perform a very useful function. I hope that this Board of Regents will give thought to this matter and will give us the benefit of its advice through discussion.

PRESIDENT MORGAN: There are two aspects of the Chairman's report; first, the liberalization of the requirements by the American Board of Internal Medicine for eligibility to examinations, and, second, proposed change in the surveying machinery. Requirements have been liberalized to the point that except for the time factor any one who practices Internal Medicine approximately ten years may come up for examination, regardless of the nature of that practice. If he follows the advice of the Board relative to type of work that he does and particular training experience through which he puts himself, he will qualify for eligibility for examination and will render himself eligible that much sooner. There has been a very marked liberalization; no one who is seriously interested in practicing Internal Medicine now is excluded from examination.

DR. MAURICE C. PINCOFFS: I think it would be a very unfortunate thing if some form of inspection and approval of the facilities for postgraduate education were given up. First, I do not think we can rely on the wisdom of these young men after an internship to judge wisely what is the best type of training. Many of them would go to hospitals in which their financial burden would be somewhat lightened, feeling that perhaps while it is not the best, the financial recompense makes it feasible for them to stay there longer; second, the Board's requirements have entered into the practice of American medicine to an astonishing extent, and I speak now from the point of view of what it has done to standards in hospitals, other than primarily in school hospitals. The strength of the present Veterans Administration is largely through an affiliation with medical schools, and thus meeting the requirements for training. They get many capable young men that they would not otherwise get. The Army has set up five General Hospitals for postgraduate training of their members, and they were forced to do this, to a certain extent, by the attitude of young men who wished to have this training in accordance with Board standards. That movement in the Army is going to have a very large influence on the medical care that some million of our young citizens receive.

It goes further than that. State institutions of all kinds are thinking seriously of how they can raise their standards. Tuberculosis hospitals in the State of Maryland are contemplating trying to raise the hospital nearest Baltimore to standards acceptable to the American Board of Internal Medicine and the American Board of Surgery. Only if they can do that, do they feel they are going to begin to solve their personnel problem.

All through the country the action of the Boards in stimulating enthusiasm in young men for better training has reacted on the level of medical care in many ways in many institutions. I feel that if it was simply said that when a candidate feels ready to come up for the examination, he can do so, and we shall depend solely on the examination, that much of the value of what has been accomplished might be lost in the next decade.

DR. IRONS: I am quite in agreement with Dr. Pincoffs. The effect of the American Board of Internal Medicine on medical education in this country is far beyond what many of us expected and beyond what the College even envisioned when the Board was established. The net result is an admirable accomplishment of the College. With respect to the requirements of the Board, they have been modified from time to time. At the beginning, the Board had to feel its way, but the present Board has enormously improved the mechanism of examination. Requirements in preparation for examination were set up almost entirely with the idea of protecting the candidate. It was recognized that what a young man does in the first five years after graduation largely determines what place he is going to occupy in the future. Therefore, the requirements of the Board have almost been made up with the idea of protecting the candidate. Several years ago the Board thought many men could obtain a good preceptorship with men well able to enlarge their studies, while working on the job. It was an admirable provision. The Board did its best to select proper preceptors, but after several years' experience learned that some of these preceptors were not carrying out the ideas of the Board and were profiteering on the candidate. There was nothing for the Board to do except abolish preceptorships for a time—you couldn't hold a trial for each preceptor. It then became necessary to set up a new group of requirements which vastly liberalized the program by which anybody can get the necessary training, if he is willing. However, the majority won't do it, under this eight and ten-year program, except the unusual case. That democratizes the examination, to meet the criticisms of the Board.

I would be much distressed to see the Board do away with all requirements, because after all we all still have a responsibility to the young man who is entering on his life work. To remove all requirements will set this matter back where it was before the Board came into existence. There has been a tremendous lot of criticism hurled against the Board—most of it unjust. Anybody who sets up standards will be subject to criticism. I want to congratulate the Board on its performance up to date, and recommend that on no account should they do away with the requirements.

DR. FRANCIS G. BLAKE: Mr. President, accepting without question the great accomplishments of the Board in raising standards in Internal Medicine and raising standards in residency training programs in an increasing number of hospitals, it seems to me, as Dr. McCann has pointed out, that there are two very urgent problems that must be met. The recent steps in liberalization seems to me to have met to a considerable extent the criticism of the lock step training program. As times goes on, there will be room for more liberalization, but, first, there are nowhere near enough approved residency trained physicians to take care of those who want to qualify themselves for recognition. Means for establishing an adequate residency training program must be provided for a large body of men.

DR. PAULLIN: Mr. Chairman, may I ask Dr. Blake to give us some statistical data on the inadequacy of approved residencies in medicine—that is, the approximate

number of people who cannot get proper training that would qualify them for certification? My impression is that the number is not very large. I hear few complaints from the surgeons who greatly outnumber the internists. I should hate to alter the past policies of the Board in this regard, even though momentarily some men cannot get training. Many Veterans' Hospitals, as now established, have met requirements; numerous hospitals in some of the cities which five years ago were not approved have raised their standards to the point where they are temporarily approved for residency training. I think it would be an awful mistake if we receded from our present standards and allowed almost anyone after ten years to take the examination. We have brought a lot of these hospitals up to a standard which they never had before. They are rendering better medical care and better medical service, and I personally doubt if the few individuals who lack the opportunity of getting training would ever qualify for certification anyhow.

DR. REGINALD FITZ: I cannot help but interject something here, for I have been a member of the Council and a member of the Board for many years, and more recently a member of the College Committee working with the Council. I think the College's considerations here are terrific. As Dr. Paullin says, there are a whole host of young men who think they want to be internists, yet not all of them are going to be capable of attaining certification. In connection with the question of establishing residencies, which has been a fine thing, there are many hospitals that think they would like to offer approved residencies, and the result is that, with the War doing away with many of the Council inspectors, we have been trying to re-establish our machinery and to resume the plan of having the participation of the Board and the Committee of the College with the Council. All of this takes a great deal of time, but is a good thing. I hope we will all be patient, because I am perfectly sure that Dr. Paullin is right when he says we will do more harm by trying to do things too quickly than by putting up with a certain number of people who do not like the way we are doing it; we must make sure we are doing it right, because there is no question in my mind that if the hospital is approved for residency training in Internal Medicine it ought to be good, and that should be determined, even though it takes an extremely long time. With the College, the Board and the American Medical Association all working together, we are doing a pretty good job.

DR. IRONS: It was the War that brought about most of the immediate troubles to the Council. The Council was cut down to one inspector a year or so ago, and now has four and is looking for more. As soon as that increased personnel begins to be felt, some of the delays and difficulties that Dr. McCann mentions will be eliminated.

DR. PINCOFFS: I feel very strongly, as has been mentioned by others, that the present system of supplying opportunities for these young men is hampered by the slowness of inspection. I also question whether the inspections are always as satisfactory as they should be. There is a question whether the young men appointed as inspectors by the Council are really the best judges always of the type of educational opportunities the hospital should provide. I have heard the criticism that the Council and the Board, through their action, have taken too dominating a position as to the character of postgraduate education leading to specialization, that there should be something, in some more official way, represented in the inspection of schools and hospitals. I was struck by Dr. McCann's suggestion of bringing in the Association of American Medical Colleges, which I think is in line with the functioning of schools having a voice in their own communities and environments, either in approving or disapproving institutions or personnel for the character of professional work. The local use of this body within its own region deserves study. They often know quite intimately the attending staff of a hospital and the standards of work done in it.

DR. DAVID P. BARR: I wish to make reference again to the question of liberalization. I hope that in the consideration of the Board one may regard or may take ac-

count of the developments in various directions which have not in the past been classified as Internal Medicine. I am thinking particularly of health services, such as are now established in many of our great universities—examples being Harvard, Cornell, Michigan, Minnesota—services in special hospitals not previously regarded as part of Internal Medicine. There I have particularly in mind the development of the Memorial Hospital, a special cancer hospital, of which there is now contemplated a very extensive development in Internal Medicine. Then, there are categories of fellowships that have not previously been thought of as Internal Medicine, and I have in mind there the psychosomatic fellowships that are being established at Cornell and Harvard. They are being established also in Cincinnati and Rochester. All of these things represent training which could at least, in some instances, be regarded as equivalents of residencies in Internal Medicine as such and, while each must be judged on its merits and the character of the training, should be taken into account.

PRESIDENT MORGAN: The Board does find itself in a very difficult position, having actually claimed the responsibility from the point of view of approving hospitals as proper places for training. It finds itself with no mechanisms to inspect those hospitals and no one obviously can develop such a mechanism unless it opens up a new field altogether, and more or less does in medicine what the College of Surgeons does in surgery. Therefore, the American Board has depended mainly upon the American Medical Association's Council and its inspectorial activities. That has been the nub of the situation, and the Council has had its difficulties. One of the most important things that the American Medical Association can do is to really energize and step up that activity and bring it to an adequately high level. If the Council is to be the actual body to survey and approve hospitals, anything that will broaden its influence will be an advantage. There is a tremendous hospitalization program under way by the Government, and it will be very much under the influence of Government agencies. The broader the point of view that can be exhibited in relation to these developments, as pointed out by Dr. Barr, the wiser will be the administration.

DR. McCANN: I think I agree, and while already on record as having been in favor of doing away with any responsibility for the previous training of candidates, I would now retreat from that position and say that I think we are committed to some sort of supervision and guidance from those agencies. The only agency that seems to be competent to do this is the American Medical Association, but I would like to urge upon the members of the Council on Medical Education and Hospitals and the Liaison Committee of this College that they explore the extent to which they can supplement their facilities by bringing in the Association of American Medical Colleges. I agree with Dr. Pincoffs that they would add some senior wisdom to the work which the inspectors of the Council do, and would provide them with certain information which would be invaluable. The Deans and Faculties know the local facilities and where qualifications are met. With the addition of this help, we could get the job done and done in a broad minded way that would let a man preparing himself as an internist take some time to train himself also in psychiatry or in pediatrics. I think the biggest lack of the internist today is of knowledge of pediatrics.

DR. PAULLIN: Has not the American Board of Internal Medicine sufficient money to finance, for two or three years, somebody to work with the Council and help the inspection program?

DR. McCANN: It might be worked out.

DR. PAULLIN: Most of the members of the Council are Deans of medical schools. Now we would have somebody approaching from the other side.

DR. McCANN: The assets of the American Board of Internal Medicine are somewhere around \$65,000.00 or \$75,000.00, which is roughly the amount of money we possess. We have increased the fee for the examination, because the costs are rising. I haven't any idea what it would cost to help the Council.

DR. FITZ: I do not think it is a question of money so much as getting personnel. Recently we had a group of about 125 veterans taking a course at Harvard and I tried to tell them what the possibilities were and what I thought was an interesting temporary job, namely, learning to analyze and inspect hospitals for those that would like to take a course in educational administration. I received about a dozen names, but in the end they all got something else that they preferred to do. It is very difficult to get first-rate men. They find greater opportunities in other fields.

DR. IRONS: The Board of Trustees of the American Medical Association is perfectly willing to furnish whatever money is necessary, but cannot get the personnel.

DR. PAULLIN: The question is of getting the American Board interested, so that they would see it in a different situation.

. . . On motion by Dr. LeRoy H. Sloan, seconded and regularly carried, it was RESOLVED, that this matter by informal discussion be explored by the College with its friends in the other organizations, the Council on Medical Education and Hospitals, the American Board of Internal Medicine and the Association of American Medical Colleges.

Dr. George Morris Piersol, Chairman, reported for the Committee on Credentials on the following matters:

The new method of circularizing members by distribution of a Roster of Candidates had proven satisfactory, but the Committee pointed out that it does not wish the return of the Roster of Candidates, but desires to have individual letters concerning any candidate about whom any Fellow has any doubt regarding his personal or professional qualifications;

The Committee on Credentials feels that the College can recognize only the regularly constituted Boards for Certification of Specialists, and cannot include various and sundry boards which may spring up among special groups;

A case in point was brought up of a former Associate who had been dropped for failure to qualify for Fellowship within the period prescribed by the By-Laws. The Committee pointed out that modification of the rules and By-Laws passed at the last Annual Session makes it impossible for such candidates who have been dropped from Associateship for reason to be nominated for direct Fellowship, but that they may be privileged to be proposed again for Associateship;

Dr. Ralf S. Martin, Portland, Maine, was reinstated to Associateship; the application of a former Fellow for reinstatement was denied;

The Committee had reviewed during the two previous days credentials of 284 candidates for Associateship and 187 candidates for Fellowship. The analyses of its recommendations follow:

Candidates for Associateship:

Recommended for Election	188
*Fellowship Candidates Recommended for Election first to Associateship	5
Deferred	52
Rejected	44
	<u>284</u> , plus *5

Candidates for Fellowship:

Recommended for Advancement to Fellowship	93
Recommended for Election Directly to Fellowship	14 107
*Recommended for Election first to Associateship	5
Deferred	58
Rejected	17
	<u>187</u>

On recommendation of the Committee and formal approval by resolution of the Board of Regents, 193 candidates were elected to Associateship and 107 candidates were elected to Fellowship (this list appeared in the January, 1948 issue of this journal).

The Committee presented the following analysis of the group of Associates elected five years previously, December 13, 1942:

Already Advanced to Fellowship	92
Dropped for Failure to Qualify	21
Time Extended Due to Military Service	39
Total Candidates Elected, 12-13-42	<u>152</u>

The names of those dropped for failure to qualify and the names of those whose Associate terms were extended, due to military service, were recorded in the formal Minutes. Likewise, the names of 7 Associates elected prior to December 13, 1942, but whose Associate terms, previously extended due to military service, had now expired, were recorded in the formal Minutes.

The Committee presented the following recommendations for later consideration by the Board of Regents, due to their involving very far-reaching and fundamental questions:

“(1) The Committee realizes that the number of applicants for admission is growing steadily. The question comes up from time to time about a candidate who is not an internist, but is a neuropsychiatrist, a dermatologist, or some other affiliated specialist. The informative booklet of the College says that membership need not be made up only of internists, but may include those properly qualified in pediatrics, neurology, psychiatry, public health, radiology, etc.

“The Committee believes it would be well to seriously consider changing our regulations and limiting membership in this organization to those who are internists and to discontinue after a certain time to take in men who are not internists, even though they be engaged in affiliated specialties. The Committee makes this recommendation primarily to further limit the size of the College. These affiliated specialties all have their own certifying boards and their own special societies, and the Committee questions whether radiologists, dermatologists, and a few others, ever take a very vital interest in the College. They are amiable and distinguished people who are in purely scientific branches, a little different from strict internal medicine.

“(2) In spite of explanatory and clear definitions which the Survey Committee made and were incorporated as amendments to our By-Laws last year, it is still a very difficult matter from data available to come to a conclusion as to who is an internist, and whether he is a man who will ultimately be able to attain certification. Even those members of the Credentials Committee who are most violent in their opposition to the recommendation some of us made, namely, that before a man should be considered as an Associate he should be certified by the American Board of Internal Medicine, have come to the conclusion that such a rule wouldn't be too objectionable, after all, if we could limit the membership of the College to those who are internists. If we decide to take only internists, we can only recognize those who have already been certified, and many difficulties would be solved and hours of debate would be eliminated.

“The Committee feels that it would make for a much stronger and more homogeneous organization.”

On the nomination and recommendation of the Committee on Masterships, Dr. William S. Middleton, Chairman, the five following Fellows were unanimously elected Masters of the College:

Dr. O. H. Perry Pepper, Philadelphia, Pa.
Dr. James E. Paullin, Atlanta, Ga.
Dr. Maurice C. Pincoffs, Baltimore, Md.
Dr. Anton J. Carlson, Chicago, Ill.
Dr. Henry A. Christian, Boston, Mass.

The report of the Committee on Public Relations was presented by Dr. Ernest E. Irons, Chairman. Among items under communications were the following:

A disciplinary recommendation from two Fellows concerning a member who had solicited x-ray contracts. The Committee considered this a matter which involves the question of ethics and recommended that it should be first dealt with by the local group and the county medical society; however, if College members in the district are not then satisfied, charges may be preferred against the member in accordance with Article XIV, Section 1 of the By-Laws of the College. (This recommendation was approved by the Regents.);

A proposal from the Hollywood Academy of Medicine that some sort of association of academies of medicine be formed for the distribution of speakers over the country. The Committee pointed out that the College already has committees to carry out its own program, and that its programs and ideals might considerably differ from those of other groups, and no action was recommended;

An inquiry from the Committee on Patents of the National Research Council, asking the attitude of the College in regard to the advisability of universities taking out patents. The Committee pointed out this question is distinctly a controversial one on which the College could make no pronouncement without extensive investigation, and that this question would seem to be without the province of the College;

Invitation from the Secretary of Labor, requesting the participation of the College on the President's Committee on "National Employ the Physically Handicapped Week." The Committee recommended that the College shall accept the invitation;

Letters and correspondence between Dr. Howard C. Naffziger, of the American College of Surgeons, and President Hugh J. Morgan, concerning means by which nursing education and increase in nursing services can be obtained. The Committee on Public Relations recognizes there is a shortage of nurses in all categories, and recommended that a Committee of three be appointed by the President of the American College of Physicians to consult with the Committee of the American Medical Association, of which Dr. Thomas Murdock, F.A.C.P., a Governor of our College, is the Chairman, and with similar committees of the American College of Surgeons and the Hospital Associations. (This was approved by the Regents by formal resolution, and President Morgan appointed Dr. Francis G. Blake, Chairman, Dr. Walter W. Palmer and Thomas Murdock.);

On the recommendation of the Committee, the dues of one Fellow were waived, due to physical disability; a former Surgeon General of the Navy, who became a Fellow of the College by reason of his position and as a service to the College, has now retired from said position and the Committee provided that his name may be automatically dropped from the Membership Roster; the resignations of Dr. William P. Chester (Associate), Detroit, Mich., and Dr. Charles A. Waters, F.A.C.P., Baltimore, Md., were accepted.

Report, Committee on Educational Policy, Dr. William S. Middleton, Chairman: The Committee on Educational Policy of necessity crosses many lines. I trust our

ruminations and recommendations may not be assumed to be presumptive in certain instances. In the first place, we were privileged to have a preview of the President's program for San Francisco. It is a very comprehensive one, and all of you will miss something if you are not in attendance. There was, furthermore, a very clear definition of the policies and program of the Committee on Postgraduate Courses. Dr. Edward L. Bortz, in attendance at that meeting, gave us an outline of the courses that had been given and of courses proposed for the spring and autumn of 1948. There is in his hands the necessity of judging of general trends; apparently, psychosomatic medicine and chemotherapy are falling somewhat in favor, and those courses have been undersubscribed in certain areas. There was, however, a suggestion that a new opportunity be offered in psychosomatic medicine under Dr. Harold G. Wolff, of New York, N. Y. This is supported by the Committee on Educational Policy. There was, furthermore, the protest of certain Fellows of the College that courses of two weeks' duration are rather extended, requiring their absence from duties, and an expression of preference in the main for courses of one week. Occasionally, by special request, for example by Dr. Robert A. Cooke, of New York, ten days will be given in Allergy for a very limited group of six to eight physicians. The policy of charging fees to foreign attendants at Postgraduate Courses was discussed, and it is the recommendation of Dr. Bortz that at the discretion of the Director of a given course, foreign guests may be free or exempt from the routine fees. This, however, would be a matter of policy that we feel the Regents should pass upon. The Committee, however, feels that it is a wise and a fair gesture to individuals coming from countries where there is a marked differential in the exchange and where it is not possible to withdraw adequate funds for participation in such programs.

In relation to the composite consideration of the program of postgraduate medical education, there was the suggestion arising out of correspondence with Dr. George R. Herrmann that a course in Cardiology be conducted by Dr. Ignacio Chavez at Mexico City during the summer of 1948, or some succeeding summer. This received the support of the Committee on Educational Policy.

The matter of fellowships under the American College of Physicians has been an expanding program, and it is the feeling of the Committee that there be given consideration to foreign fellowships, that there be no limitation to American centers or of American leaders, but that our candidates be considered for training in foreign areas. This should probably be considered by the Committee on Fellowships and Awards.

There was latterly the consideration of the correspondence of Dr. Noble Wiley Jones relative to exchange professorships with Australia, but the sense of our Committee was that we might properly enter upon this project conservatively through the recommendation to the Regents that there be invited from time to time from any foreign country distinguished guests who would address the American College of Physicians at its Annual Meeting. It was the further suggestion that such individuals, if known to the College at large, might become the guest or visiting professors to any one of our medical colleges. This would, of course, be the responsibility of the respective universities, and not of the American College of Physicians.

There was lastly the advice to the Regents that it is the sense of the Committee on Educational Policy that a gracious gesture would be made in inviting several English speaking colleagues to attend our Annual Meetings.

. . . On motion by Dr. William D. Stroud, regularly seconded and carried, the report and recommendations of the Committee on Educational Policy were approved.

Report, Editor, ANNALS OF INTERNAL MEDICINE, Dr. Maurice C. Pincoffs: The ANNALS, judging by its circulation, is meeting the approval of the profession, to the satisfaction of the Editor, and, I hope, to the members of the Board. Our chief

problem at the present time is the paper shortage, which we had hoped would be alleviated long ago, but which is about as serious as it ever was. Consequently, the numbers of the ANNALS are slimmer than we would like to have them, and slimmer than the material that comes in would warrant. The manuscripts now received show in general a much higher standard of quality, and there is a larger number than even before the War. On the average, we receive about thirty-five papers and fifteen case reports a month. We publish about eight general papers and from three to five case reports. We have made a special effort to raise the standard of our editorials. We have gone afield from the Editors, although Dr. Clough contributes very heavily, to men in special fields to write editorials, and I hope they are occasionally read and considered a valuable feature of the journal. Any question of expansion of the ANNALS itself, or any other publication that the College might wish to undertake, must be deferred until it would be feasible from the point of view of facilities. The Annals Committee has discussed those matters in a tentative way. One that occurred to us for the future is the possibility of publishing all the Morning Lectures. At present we are able to accept only a few Morning Lectures. These Lectures are generally too lengthy, and sometimes it is difficult to get all the manuscripts. However, there is a demand for them, and some of them are very valuable.

We encounter trouble in getting out the journal on time, and I think my office has to take part of the onus for that, but it also lies to some extent with the difficulties that our excellent printers, the Lancaster Press, have been having in War time and since. The speed with which they can convert a manuscript into a galley and turn the galley into page proof is distinctly less than formerly, and they are operating on a very tight schedule. They print a number of journals, and we, therefore, share the difficulty of getting our manuscripts through sufficiently far in advance. We now have in their hands, for example, all the accepted material for January and part of February, but even so we shall find that it is going to be difficult to get out these issues by the middle of the respective months. Progress is being made on getting back on schedule, and I hope that in 1948 we shall accomplish our aims in that direction.

Dr. Edward L. Bortz, Chairman, reported for the Advisory Committee on Postgraduate Courses, pointing out that during 1947 nineteen courses were given with an attendance of more than one thousand physicians. All courses had been substantially successful, and the Committee had noted a trend in interest, probably stimulated by the American Board of Internal Medicine, in returning to the refreshing experience in the basic studies. The most popular course the College had given was one on the Physiological Basis for Internal Medicine at Philadelphia, and the Committee was planning other similar courses in other parts of the country. Dr. Bortz then presented the schedule of Postgraduate Courses proposed for the spring of 1948 (this list already printed elsewhere in the ANNALS), and he proceeded to emphasize the importance of physicians acquainting themselves with the medical aspects of radioactivity. He said in part, "That field is of the greatest importance clinically, basically and from the standpoint of industrial hazards, because one of the most significant pronouncements that has been made since the end of the War was that of the distribution of Radioactive Isotopes at the Fourth International Cancer Congress in St. Louis during September. As these Radio Isotopes are being distributed, qualified personnel throughout the world for transit and handling at the site of origin where they are made and where they are being studied in industry is necessary; the field is expanding so rapidly, and the medical profession knows practically nothing about it. Doctors are not yet cognizant of the immediate importance of this field. When one considers the possibilities that may develop in our country in the future, one can appreciate the tremendous responsibility that might fall on the shoulders of the medical profession. We should awaken to the importance of having a sound understanding of the management of casualties due to radioactive substances. The course the College has

arranged through the courtesy and coöperation of the Navy, will present an unusual opportunity for members to become better informed about radioactive substances and the biological effects of exposure to them."

Dr. Bortz further pointed out that his Committee and the Executive Secretary are studying the schedule of courses for the autumn of 1948, and even looking forward to two or three years ahead, noting courses that ought to be fitted into the College program at the appropriate time.

(The Board of Regents by resolution approved the report and the schedule of courses for the spring of 1948.)

Report, Conference Committee on Graduate Training in Medicine, Dr. Reginald Fitz, Chairman: Mr. President and members of the Board, the resolution introduced by Dr. Sloan and already passed epitomized the work of the Conference Committee. For the sake of the record, the Committee would like to report that it met both with the Council on Medical Education and Hospitals of the American Medical Association and with the American Board of Internal Medicine. The idea of having advice available from the College to these two bodies seemed to have been well received, though exactly how the College can contribute most appropriately is still undetermined. This report is submitted as one for progress and contains no recommendations.

. . . On motion by Dr. Reginald Fitz, regularly seconded and carried, the report was accepted. . . .

Report, Committee on Fellowships and Awards, Dr. Reginald Fitz, Chairman: Since the last meeting of the Board of Regents, the Committee on Fellowships and Awards has held several conferences by mail. It has selected Dr. Ernest W. Goodpasture, of Vanderbilt University, to receive the John Phillips Memorial Award for 1948. Not only has his work in virology been outstanding, but as a teacher, he has proved to be an inspiring leader to generations of medical students. The Committee believes his work has had a direct bearing upon the advancement of clinical science in this country, and that in every way he deserves the award.

A year ago the Board of Regents ruled that the Committee, after obtaining the advice of the President and others, should nominate to the Board at least four months before the next Annual Session a candidate to receive the James D. Bruce Memorial Award and to deliver the James D. Bruce Lecture. The candidate so nominated must be eminent in any of the many divisions of preventive medicine. The Committee, supported by the President, now nominates for this distinction in 1948, Dr. James S. Simmons, a Fellow of the College, formerly Chief of Preventive Medicine Service in the Surgeon General's Office, and the Army member of the President's Committee on Medical Research, O.S.R.D., and at present Dean of Harvard School of Public Health.

The Committee has made a study of the accomplishments of the College's Research Fellows. Of 16 Fellows appointed up to the beginning of the War, one has become a Professor of Medicine, one an Associate Professor, six Assistant Professors in medical faculties, and almost all the rest occupy positions weighted with research or teaching responsibilities. Such a record is impressive, yet the question arose as to whether candidates were being selected from a sufficiently wide field. With this thought in mind this year, the Committee has widely circulated announcements concerning the Fellowships. Thirty-seven applications from over the country were filed before the arbitrarily stipulated deadline of November 1, a far larger number than ever before. These applications have been sifted with all possible care, and from the list the Committee now recommends that seven Fellows be appointed to begin work on July 1, 1948, namely:

(1) James G. Campbell, a graduate of McGill University; \$3,200.00.

(2). Frank H. Gardner, a graduate of Northwestern University; \$2,200.00.

- (3) Joseph E. Gianairacusa, a graduate of the University of California; \$3,200.00.
- (4) Samuel P. Martin, a graduate of Washington University; \$3,200.00.
- (5) Peritz Scheinberg, a graduate of Emory University; \$3,000.00.
- (6) Lutfu L. Uzman, a graduate of Harvard University; \$2,200.00.
- (7) John M. Weller, a graduate of Harvard University; \$3,200.00.

On the first day of July, 1948, \$10,266.67 will remain in the unexpended Research Fellowship Fund. The Committee asks for an additional appropriation of \$10,200.00, making an entirely available fund of \$20,466.67, to be available for Fellowships from July 1, 1948, to June 30, 1949.

The candidates nominated are young men, and several have had their normal careers interrupted by periods of military service. The Committee believes that they represent a group of unusual promise and seriousness of purpose. The differences in stipend take into consideration the financial needs of each candidate and the number of his dependents.

In accordance with the vote of the Board of Regents on April 29, 1947, the Committee has chosen Dr. John M. Weller to be known as the Alfred Stengel Research Fellow of the College for 1948. Of the Fellows nominated, he appears to offer promise of attaining great distinction in investigation and teaching, and as a clinician. I move the acceptance of this report and the adoption of the recommendations of the Committee.

. . . Motion was duly seconded and carried. . . .

Dr. Francis G. Blake, Chairman, reported for the Committee on the ANNALS OF INTERNAL MEDICINE, making the following points:

- (1) The Committee, with the authorization of the Executive Committee, had approved the increase of approximately 8 per cent in the printing costs from August 1, 1947, amounting to approximately \$2,500.00 per annum currently;
- (2) The last two complete volumes, XXV and XXVI, for the year ending June 30, 1947, had produced a surplus of \$32,328.49, and the average circulation had increased nearly 2,000 copies per month;
- (3) The Committee felt the content of the ANNALS with respect to original articles, case reports and editorials had been highly satisfactory; the number of pages devoted to news notes and miscellaneous material had been reduced from 400 pages to 326 pages; the Editor had reported an adequate and satisfactory supply of material for publication; increase in the size of the journal has been restricted solely due to limitation of available paper, but as soon as additional supplies are available, the number of pages per issue shall be increased; the Committee recommends a better quality of paper as soon as it is available;
- (4) A special effort should be made to restore the regular publication schedule, so that the ANNALS shall appear by the sixteenth of each month;
- (5) The Committee had reviewed the Editor's budget, and had recommended its approval to the Finance Committee.

(The Regents, by resolution, accepted and approved the report.)

Report, House Committee, Dr. William D. Stroud, Chairman; Mr. President and members of the Board of Regents, it is recommended by the House Committee that the Board of Regents formally authorize the setting up of a Building Fund Reserve for the following, which has been tentatively authorized and approved by the Board at the meeting of April 27, 1947. This is not a budget appropriation per se and is not chargeable against 1948 income.

Contract with R. M. Shoemaker Company for construction of new addition to College Headquarters Building	\$48,880.00
Less: Reduction for using Indiana limestone instead of architectural tile	900.00

\$47,980.00

Architect's Fee, 6% (Trumbauer Co.)	2,878.80
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Extras (Estimated):

Laying New Telephone Conduit	\$ 125.00	
Lighting Fixtures	800.00	
Floor Covering, General Office (plastic tile or rubber)	1,000.00	
Miscellaneous (unforeseen emergencies)	2,216.20	4,141.20
		<hr/>
		\$55,000.00

... On motion by Dr. William D. Stroud, regularly seconded and carried, the above recommendation was unanimously approved. . . .

The House Committee was consulted about the possibility of providing at the College Headquarters temporary space for the American Academy of Allergy, on a donation basis of an appropriate fee, possibly from \$70.00 to \$80.00 per month. This would not be on a true rental basis. The Committee met with the Executive Secretary, who feels that after we occupy the new wing of the new Building, two rooms on the second floor might be made available to the Academy on a "cancellable basis," satisfactory to both organizations. The American Academy of Allergy is considering moving their headquarters from New York to Philadelphia, but have not actually come to a conclusion.

DR. PAULLIN: Should not any such arrangement for occupying space be subject to cancellation, possibly on sixty days' notice?

DR. FITZ: Is there any question of the legality of the procedure. I should like to make sure that any arrangement is above reproach.

DR. TENNEY: The New York Academy of Medicine houses several other societies in its Building, but that does not affect its income tax status.

PRESIDENT MORGAN: I would assume that any arrangement that is worked out to implement the motion we are considering will be done with the advice of the attorneys of the College.

... On motion by Dr. William D. Stroud, regularly seconded and carried, this second portion of the report of the House Committee was approved. . . .

Report of the Treasurer, Dr. William D. Stroud: On October 31, 1947, the Cash Balance of the College was as follows:

Endowment Fund	\$ 3,013.27
General Fund	124,725.23
	<hr/>
	\$127,738.50
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The Finance Committee will make recommendations concerning the investment of the balance in the Endowment Fund and of \$10,000.00 additional from the General Fund.

The Finance Committee will report the record of security transactions since the last meeting of this Board.

Present security holdings of the College are as follows:

	<i>Book Value</i>	<i>Market Value</i>	<i>Appreciation</i>
Endowment Fund	\$253,941.62	\$266,397.75	\$12,456.13
General Fund	146,441.18	163,211.25	16,770.07
	<u>\$400,382.80</u>	<u>\$429,609.00</u>	<u>\$29,226.20</u>

The approximate annual cash income from these securities amounts to \$16,000.00, an average yield of 3.84 per cent.

The services of our Investment Counselor, Drexel & Co., appear to your Treasurer to be entirely satisfactory. At the last meeting of the Board of Regents, the Treasurer was instructed to attempt to persuade the Investment Counselor to be more conservative in their proposed increased service charge, and I am glad to report that effective July 1, 1947, the charge was increased to \$300.00 per year, rather than to \$400.00, as they had proposed earlier. The arrangement is subject to termination by either party at any time, and in all other respects the agreement remains in effect as first made on December 30, 1940.

. . . On motion by Dr. William D. Stroud, regularly seconded and carried, the report was accepted. . . .

Report, Committee on Finance, Dr. Charles F. Tenney, Chairman: The Committee on Finance met with the Executive Secretary and Treasurer on November 22, 1947, and reports as follows:

(1) The following transactions have been executed since the last meeting of the Board of Regents:

Sold

Endowment Fund

	<i>Cost</i>	<i>Sold For</i>	<i>Gain</i>
7-10-47 5,000 Chicago & Western Indiana Railroad Co., Consolidated, 4s, due 1952	\$5,225.25	\$5,241.25	\$16.00

Called

General Fund

	<i>Cost</i>	<i>Called For</i>	<i>Gain</i>
9-30-47 50 Shares, American Brake Shoe & Foundry Co., 5¼%, Cum.	\$6,163.60	\$6,250.00	\$86.40

Purchases

Endowment Fund

7-10-47 50 Shares, Atlantic Refining Co., \$3.75, Pfd., Cum., "B" ..	\$5,080.00
7-10-47 20 Shares, Liggett & Myers Tobacco Co., Common "B" ..	1,830.00
7-11-47 6,000 United States of America Savings Bonds, 2½s, Series "G", due July 1, 1959	6,000.00
10- 6-47 20 Shares, Texas Company	900.00

General Fund

10-21-47 50 Shares, New York Power & Light, \$3.90, Pfd.	5,067.50
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(2) The Committee examined in detail the analysis of the College holdings by its Investment Counselor, Drexel & Co., and approves their recommendations for the following:

For the General Fund:

5,000 New York, New Haven and Hartford Railroad Co., Harlem River & Port Chester Division, 4s, 5-1-54, at par
20 Shares, E. I. du Pont de Nemours & Co., common, at 189
Also, the conversion of Phillips Petroleum Co. rights to appropriate stock purchases in the approximate amount of \$1,300.00.

For the Endowment Fund:

80 Shares, General Electric Co., Capital Stock, at approximately 37

The Committee examined in detail the operating statements and budgets prepared by the Executive Secretary and herewith submitted to the Board. The first three pages of the operating statements represent experience through October 31, 1947, and pages four and five represent estimated income and expenditures to the end of the year. It is anticipated from these statements that there will be a surplus for 1947, exclusive of the building program, of approximately \$48,000.00. It may be pointed out that the income for 1947 was materially greater than anticipated for the following reasons:

- (1) The Board of Regents returned the rate of dues to the original level of several years ago, which resulted in an increase from that source of \$13,000.00.
- (2) There were more members inducted to Fellowship, with an increase in the Initiation Fee account.
- (3) The income from investments, likewise, was greater than anticipated.
- (4) Subscriptions to the journal increased more than \$14,000.00 over anticipations.
- (5) A phenomenal number of Fellows subscribed to Life Membership.

(Dr. Tenney reviewed in detail the various departmental budgets, and after certain adjustments were made by the Board of Regents, a budget providing an estimated income of \$193,830.00 and an estimated expenditure of \$152,644.10 was adopted. Entirely separate from that budget was the appropriation to the College Building Fund of \$55,000.00 authorized during 1947, but payable during 1948. The entire report, the financial statements for 1947 and the budgets for 1948 were by resolution approved by the Regents.)

Report, Joint Committee for the Coördination of Medical Activities, Dr. Ernest E. Irons, Chairman: This Committee has continued its meetings. About a year ago we asked the members whether it would be wise to discontinue the activities of the Committee, but there was a general protest on the part of almost everyone, and the feeling was expressed there would be certain advantages in having the general problems affecting medicine receive discussion and comment by all the member organizations, including the hospital associations, one of the large funds, the Armed Services, the Public Health Service, the Federal Security Administration, and practically all large organizations that have an interest in medicine. The College is represented by Dr. Walter L. Palmer and myself. The Minutes of the meetings are printed in the Journal of the American Medical Association, although occasionally somewhat delayed, due to paper shortages and also by reason of the fact that all of these Minutes must go to each representative for comment and approval before publication. On the whole, I think there is a distinct value attached to this Committee. It is no expense to the College.

PRESIDENT MORGAN: The last Committee report is that of the Consulting Committee on the Annual Sessions. I am glad to report that the General Sessions and

Morning Lectures have been arranged, and there remains only one or two vacant assignments to be settled.

(Dr. Morgan passed out copies of his Program.)

Dr. Alan Gregg, Director of the Medical Science Division of the Rockefeller Foundation, will be the Convocational Lecturer. I will now ask Doctors Kerr and Falconer, joint General Chairmen, for their reports.

DR. WILLIAM J. KERR: Mr. President, Officers and Regents, Dr. Morgan's program, as he has announced it, appears to us to be quite outstanding. Dr. Falconer and I have been working on the Panels and on the Clinics. The Panels are going to be held each noon, as in recent years, and the Morning Lectures will be confined to two mornings, with a double series each morning, and the Clinics will be consolidated into two mornings, held in several of the hospitals in San Francisco. This year the Clinics will actually be clinics. We are not planning to give any other demonstrations, or to carry on further series of lectures, etc., but everyone participating in the Clinic Sessions will be expected to discuss the problems of patients, and that will be the keynote. The Panels have been well worked up, although I cannot give you all the details at the moment. They will cover the main problems of medicine.

We are emphasizing, as we should in our part of the country, two features—one on infectious diseases, in which we have some preëminence in that part of the country, and the other on radioactive elements of the isotopes. This is one of the great important areas of knowledge in medical practice at the present time, and unless we are abreast of what is going on in that field, we shall be quite remiss in bringing things to the attention of the members of the College.

We hope we shall have a large attendance. In 1932, when the College last met in San Francisco, we were in the depths of the great depression, and there were only two hundred or so members who came to California from East of the Rocky Mountains. I am sure that will not be repeated this time. We are prepared to show all the members what is going on on the Pacific Coast.

Some of the details of entertainment have not yet been concluded. 1948 marks the centenary of the discovery of gold in California, and we think there is still gold "in them thar hills," and we are going to feature this celebration to some extent. Long years ago we had a visitor in California by the name of Robert Louis Stevenson, who was a great friend of the physician, and who had good reason to know physicians. It may be possible to do something in a small way to honor the name of that great man. At any rate, we hope to have some things in the way of entertainment which are unique. We may even be undignified at times, but your President has acquiesced and encouraged us to give you a good time. Dr. Falconer had to leave for a plane, and asked me to report for him as well.

Those of you who are coming by special train, or otherwise, may be able to visit some of the National Parks, or the redwood section of California, or the Yosemite; there are many things worth seeing if you have not seen them before.

PRESIDENT MORGAN: Some members have repeatedly asked that some method be worked out to record the Panel Discussions. The Panels are really one of the most interesting features of the Annual Session. They are informal, conducted by experts and are extremely informative. I would like to suggest that they may be reported in the ANNALS. That raises a question that has come up many times in our meetings, which, up to the present time, has not been solved. Everyone knows it is a fine idea, but it has produced problems that have been very difficult to meet. It is only a matter of recording what is said, and I suggest, Dr. Kerr, that you look into the possibility of using the soundsciber, or other recording device, if not for all the Panels, at least for certain Panels that you know are going to be of great interest. The record will have to be edited, and that might be an after meeting responsibility which you could pass on to some of the members of your department. It may cost us some money, but I

think we should attempt to determine if this can be successfully done. We will now hear the arrangements made by the Executive Secretary for the meeting.

Mr. Loveland reported that he had spent some days in San Francisco during June, making the necessary general arrangements. He reported on the matter of hotels, meeting rooms, the Technical Exhibit, meeting schedules of the Regents, Governors and Committees, the special trains to San Francisco, the post-convention trip to Hawaii, etc. There followed a discussion of the schedule of meetings of the Board of Governors and the Board of Regents, and it was finally agreed that the various Committees would meet on Saturday and Sunday morning, April 17-18, and the Board of Regents and Board of Governors would hold a joint executive session on Sunday afternoon, April 18, and that the schedule of other meetings of the two Boards be continued as heretofore. It was also suggested that the Chairman of the Committee on Credentials appear before a meeting of the Board of Governors to acquaint that Board with the problems and difficulties of handling candidates for membership.

By resolution, the meeting adjourned at 2:40 p. m.

Attest: E. R. LOVELAND,

Secretary

OBITUARIES

DR. MARION HERBERT BARKER

M. Herbert Barker, M.S., M.D., F.A.C.P., of Chicago, Ill., died suddenly on August 14, 1947, of a subarachnoid hemorrhage.

Dr. Barker was born in 1899 at Villisca, Iowa. He received a B.S. from the University of South Dakota in 1923, an M.D. from Rush Medical College in 1925, and an M.S. in Physiology from Northwestern University in 1930. His training included a two-year internship at Wesley Memorial Hospital, Chicago, two years as assistant resident at the Peter Bent Brigham Hospital in Boston, and two years as resident at the Passavant Memorial Hospital in Chicago. He became an attending physician at the last institution in 1931 when he entered private practice.

Throughout his professional career Dr. Barker was active in teaching and research. At the time of his death he was Associate Professor of Medicine in the Northwestern University Medical School. His primary interest was in the field of cardiovascular-renal disease, although during the war he was responsible for much of the work done by the Army on infectious hepatitis. He published over 40 papers, many representing original contributions.

During World War I Dr. Barker served in the Marine Corps. In World War II he had nearly four years of active duty, two and one-half of which were in the Mediterranean Theater. As a Lieutenant Colonel and later as a Colonel he was Chief of Medicine in the 12th General Hospital. In 1944 he was appointed special consultant to the Theater Surgeon and received the Legion of Merit for his work on infectious hepatitis.

Dr. Barker was a member of many medical organizations including the Chicago Society of Internal Medicine, Chicago Institute of Medicine, Chicago Society of Medical History, Central Society for Clinical Research, Central Clinical Research Club, American Heart Association (Chairman of Peripheral Vascular Section in 1946), American Society for the Study of Arteriosclerosis (founding member), fellow of the American Medical Association, fellow of the American College of Physicians, and member of the Cardiac Society of Great Britain. In addition he was Chairman of the Committee for Nomenclature of Renal Vascular Disease, Regional Consultant in Internal Medicine to the Surgeon General of the United States Army and Chairman of the Board for the Study of Hepatitis, member of the Sub-committee on Diseases of the Liver of the National Research Council. He was a diplomate of the American Board of Internal Medicine, certified in internal medicine and cardiovascular disease.

Dr. Barker was endowed with tireless energy and vitality. He was not only an able physician and teacher but an astute investigator. In addition he was concerned with many organizational activities. His enthusiasm and vision made him a valued counselor. His loss will be keenly felt, not only in Chicago and among his friends, but among his many colleagues throughout the country.

RICHARD B. CAPPS, M.D., F.A.C.P.

DR. CHARLES J. BLOOM

Dr. Charles J. Bloom, a Fellow of the College since 1928, died at Touro Infirmary, New Orleans, on August 29, 1947, of heart disease.

Dr. Bloom, son of Albert and Rose (Dreyfous) Bloom, was born in New Orleans, October 23, 1886. He received his primary and secondary education in the public schools of New Orleans and attended Tulane University of Louisiana (B.S., 1908, and M.D., 1912). He served an externship at Charity Hospital of Louisiana, 1909-

1910, and an internship at Touro Infirmary, 1912-1914. He attended Harvard University for postgraduate courses 1914-1916.

His teaching, which covered a period of 35 years, began during his student days at Tulane as Instructor in Zoology, 1907, and Lecturer in Biology, 1908. He was Assistant in Hygiene in the Tulane School of Medicine, 1912-1914; Assistant in the laboratory of Hygiene and Clinical Assistant in Diseases of Children, 1914-1916; Instructor in Pediatrics, 1919-1920. In the Tulane Postgraduate School, where he became head of the Department of Pediatrics, he was Clinical Assistant in Diseases of Children, 1916-1918; Assistant Professor of Diseases of Children, 1918-1919; Professor of Diseases of Children, 1919-1925; Professor of Pediatrics, 1925 until his resignation, June 30, 1937. At Louisiana State University School of Medicine he was Professor of Pediatrics and head of the Postgraduate Department (1937-1939). He was also a member of the faculty of the Southern Pediatric Seminar, Saluda, N. C. (1924-1942).

He had served in attending or consultant capacity on the staff of practically every hospital in New Orleans, and at the time of his death was on the staffs of Charity Hospital of Louisiana (head of the Independent Pediatric Service), Touro Infirmary (former Secretary), Baptist Hospital, Lakeshore Hospital, French Hospital (Consultant), and Flint Goodridge Hospital of Dillard University (Consultant). Among his community interests he founded the Magnolia School for exceptional children in 1934 and served as its General Chairman. During the first World War he held the rank of First Lieutenant in the Medical Reserve Corps.

He was a member of the Orleans Parish and Louisiana State Medical Societies, the American Medical Association, Southern Medical Association, Louisiana State Pediatric Society; American Academy of Pediatrics, Pure Milk Society of New Orleans (board member), Society of Mental Hygiene, Beta Theta Pi, Nu Sigma Nu, Kappa Delta Phi, Alpha Omega Alpha, Stars and Bars, Tulane Alumni Association (one of representatives from the School of Medicine on the Executive Committee, 1942-1946).

Among his many contributions to medical literature, his book on "The Care and Feeding of Babies in Warm Climates" (1922, revised 1937) was widely used.

EDGAR HULL, M.D., F.A.C.P.,
Governor for Louisiana

DR. GEORGE CUMMINGS BOWER

George Cummings Bower, M.D., F.A.C.P., was born at Blasdell, N. Y., September 28, 1898. His medical degree was taken in the University of Buffalo in 1922, following which he interned in the Erie County and Deaconess Hospitals in Buffalo. He became Assistant Physician in the Willard State Hospital, Willard, N. Y., from 1924 to 1928, and subsequently served as Pathologist and Director of Clinical Laboratory in the Marcy State Hospital, Marcy, N. Y., from 1933 until his death. Dr. Bower was a Diplomate of the American Board of Pathology.

Dr. Bower was elected a Fellow of the American College of Physicians in 1934. He was also a member of the Geneva Academy of Medicine, the Seneca County and New York State Medical Societies, the New York State Society of Pathologists, and the American Medical Association.

Dr. Bower was highly respected for his scientific knowledge by his associates at the Marcy State Hospital. In his death the hospital has lost a very capable and efficient pathologist.

EDWARD C. REIFENSTEIN, SR., M.D., F.A.C.P.,
Governor for Western New York

DR. PERCY TILSON MAGAN

Percy Tilson Magan, M.D., F.A.C.P., was born on November 13, 1867, at Marlefield House in the County of Wexford, Ireland. He died on December 16, 1947, from a heart attack which was the terminal incident of a long illness.

At the age of seventeen years, Percy Magan, the eldest son and potential heir to an estate of considerable worth, left his home in Ireland, and came to America, landing on the day of Grant Ward Panic in May of 1884. Though times were hard and his economic status was not particularly good, he had previously decided to work out his own problems and to plan his own career. Traveling farther west to Nebraska, he worked as a farmhand for over a year.

While he had received a sound preliminary education at St. George's School in Huntingdon, England, he had become resentful of the strict discipline of the educational system and had no particular desire to receive further formal education. He became acquainted with many Seventh-day Adventists and eventually joined that church, in the interest of which he devoted all of his time and energy throughout the rest of his active life. His sincerity and devotion were exemplified by his adherence to his faith even though he was disinherited by his father. In 1888 he entered the Battle Creek College in Battle Creek, Mich., from which he graduated in 1893. Soon thereafter he accompanied S. N. Haskell, a leader in the Adventist Church, in a trip around the world to find suitable locations for the establishment of mission stations. He was Professor of History and the Bible in the Battle Creek College from 1891 to 1901, and established a reputation as a great teacher. Later, as its Dean, he entered the field of administration which he followed for the rest of his life. His reputation as a school administrator became widely recognized. In consideration of certain problems which were developing at the Battle Creek College, he and E. A. Sutherland were instrumental in moving the College to Berrien Springs, Mich.; it has since grown to be one of the strongest colleges in the Adventist educational system.

Dr. Magan and his close friend, E. A. Sutherland, developed a strong desire to establish self-supporting medical missionary work in the neglected South. In order to become better qualified to attain the objectives of such a project, both men decided upon a medical education. Dr. Magan received the M.D. degree cum laude in 1914 from the University of Tennessee College of Medicine. Doctors Magan and Sutherland then established a medical institution in connection with the Church's school at Madison, Tenn. This is still operating, and from this center there have developed some thirty smaller self-supporting rural schools and medical centers.

In the meantime, the College of Medical Evangelists had been started, and, on the recommendation of President Newton Evans, Dr. Magan was appointed Dean in 1915. He was made president in 1928 and president emeritus in 1942.

In less than two years, he succeeded in raising the rating of the school from class C to class B. The College continued to grow, its foundations have become more secure, and Dr. Magan is credited with bringing it to its present place among the medical schools of the land.

Dr. Magan was well known among American and British medical educators and leaders. Membership in many professional societies indicated his interest in the general field of medicine. These included the Chairmanship of the Anatomy Board, southern division, Department of Public Health, California; trustee, Medical Board of Los Angeles County General Hospital; member, Board of Trustees, Public Health League of California; Fellow, American Medical Association, Society of American Bacteriologists, American Hospital Association, League for Conservation of Public Health, National Tuberculosis Association, American Cancer Foundation, Southern California Medical Association, Clinical and Pathological Society of Los Angeles; ex-Vice President, California Medical Association; Trustee, Los Angeles County

Medical Association; Fellow, American College of Physicians, 1929. He was also editor of the Health Magazine.

Dr. Magan was an indefatigable worker, a man of strong convictions and of extraordinary ability. He devoted his life to the cause, and the things which he has said and the influence which he has had in the College of Medical Evangelists and in the lives of many who have been associated with him will long be remembered.

W. E. MACPHERSON, M.D., F.A.C.P.

DR. JOHN NATHAN SIMPSON

John Nathan Simpson, M.D., F.A.C.P., died on November 23, 1947, at the General Hospital, Morgantown, W. Va., following several years of illness. Dr. Simpson was 78 years old.

Born in Morrison, Ill., March 19, 1869, Dr. Simpson was a graduate of Peabody College for Teachers, Nashville, Tenn. (A.B., 1891) and of the Johns Hopkins University (M.D., 1902). In 1902 he founded the College of Medicine of West Virginia University as an organized two-year school. Prior to that time the University had offered courses in anatomy, physiology, and hygiene. Dr. Simpson served the College of Medicine as Professor of Anatomy and Physiology, as Professor of Medicine, and as Dean, until 1935 when he became Professor Emeritus and Dean Emeritus. In 1906 he studied in Paris and Vienna.

Dr. Simpson was Director of the Hygiene Laboratory of the State Department of Health from 1913 to 1917.

Dr. Simpson's society memberships included the American Academy of Medicine, American Medical Association, American Association for the Advancement of Science, Southern, Mongolia County and West Virginia State Medical Associations; he was president of the latter Society in 1923.

Dr. Simpson was one of the early members of the American College of Physicians, having been elected a Fellow in it and a member of the American Congress on Internal Medicine in 1921. In 1922 he became a member of the first Board of Governors of the College and served as Governor for West Virginia from that date to 1936.

DR. THOMAS E. WILLIAMS

Dr. Thomas E. Williams, of Shreveport, La., a Fellow of the American College of Physicians since 1926, died on October 4, 1947, of carcinoma of the prostate.

A native of Hillsboro, Ohio, and a graduate of the Jefferson Medical College of Philadelphia, Dr. Williams began practice in Marshall, Tex., but afterwards moved to Shreveport, where he was active in the medical and civic affairs of that city for many years. He enjoyed a large medical practice, but was also active as a member of the visiting staff of the Shreveport Charity Hospital. He was one of the founders of the Tri-State Hospital, and was chief of the medical staff of the Tri-State Clinic.

Dr. Williams was a member of the Shreveport, Louisiana State and Tri-State Medical Societies, the Southern Medical Association, and a Fellow of the American Medical Association. In 1926 he was elected a member of the American Congress on Internal Medicine.

Because of ill health Dr. Williams had been in semi-retirement for several years before his death.

EDGAR HULL, M.D., F.A.C.P.,
Governor for Louisiana

PROGRAM

THE AMERICAN COLLEGE OF PHYSICIANS

Twenty-Ninth Annual Session

SAN FRANCISCO, CALIF.

April 19-23, 1948

GENERAL SESSIONS AND LECTURES

Hugh J. Morgan, President

GENERAL CHAIRMEN

William J. Kerr and Ernest H. Falconer

HONORARY COMMITTEE

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George Blumer, Pasadena	Herbert C. Moffitt, San Francisco
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T. Homer Coffen, Portland, Ore.	Robert T. Sutherland, Oakland
George Dock, Pasadena	Roy E. Thomas, Los Angeles
James J. Waring, Denver	

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George Anderson.....	Washington
Harry L. Arnold.....	Hawaii
Robert O. Brown.....	New Mexico
Ward Darley.....	Colorado
Leland P. Hawkins.....	California (Southern)
Ernest D. Hitchcock.....	Montana & Wyoming
Fred G. Holmes.....	Arizona
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Samuel M. Poindexter.....	Idaho
Homér P. Rush.....	Oregon
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Dwight L. Wilbur, Chairman

George D. Barnett, San Francisco Hospital (Stanford Service)
Arthur L. Bloomfield, Stanford University Hospital, San Francisco
LeRoy H. Briggs, San Francisco Hospital (University of California Service)
Edwin L. Bruck, St. Luke's Hospital, San Francisco
Anthony B. Diepenbrock, St. Mary's Hospital, San Francisco

Earl F. Evans, Captain, (MC), U.S.N., U. S. Naval Hospital, Oakland
 Mack M. Green, Colonel, (MC), U.S.A., Letterman General Hospital, San Francisco
 Gordon E. Hein, Veterans Administration, San Francisco
 Stacy R. Mettier, University of California Hospital, San Francisco
 John J. Sampson, Mount Zion Hospital, San Francisco
 Edward B. Shaw, Children's Hospital, San Francisco
 H. Clare Shepardson, Franklin Hospital, San Francisco
 Michael B. Shimkin, Laguna Honda Hospital, San Francisco

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Sidney J. Shipman, Chairman

Theodore L. Althausen

J. C. Geiger

Harold G. Trimble

COMMITTEE ON HOTELS AND TRANSPORTATION

George S. Johnson, Chairman

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George Morris Piersol, Chairman

Thomas Klein

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Mrs. Raymond J. Reitzel
Mrs. Albert H. Rowe
Mrs. H. Clare Shepardson
Mrs. Maurice Sokolow
Mrs. Fletcher B. Taylor
Mrs. Harold G. Trimble

INVITATION

Sixteen eventful years have elapsed since San Francisco was host to the American College of Physicians, in April, 1932. A very special and cordial welcome has accumulated during this period, and is extended to the members of the College for its Twenty-ninth Annual Session.

San Francisco as a civic institution, the San Francisco and Alameda County Medical Societies, the California Medical Society, the California Academy of Medicine, the medical schools and the hospitals of San Francisco and the Bay Region send greetings and are prepared to extend their facilities to the members and guests.

San Francisco has two Class A medical schools, Stanford University School of Medicine and the University of California Medical School. The former is the outgrowth of the old University of the Pacific founded by Elias S. Cooper in 1858. In 1882 Doctor Levi Cooper Lane built the first of the present medical school buildings on land donated by himself, and later constructed Lane Hospital. In 1908 this property was transferred to Leland Stanford Junior University and forms a nucleus of the present medical school. The University of California Medical School was founded by Doctor H. H. Toland in 1864. He transferred Toland Hall to the Regents of the University in 1873. It was not until 1902 that the Medical Department actually became part of the University. The campus of the Leland Stanford Junior University lies adjacent to the city of Palo Alto, 30 miles from San Francisco. The campus and buildings are readily accessible from the standpoint of transportation facilities and make a very interesting trip. The academic departments of the University of California are located in Berkeley. This campus is readily accessible and makes an interesting trip via the San Francisco-Oakland Bridge. In addition to the two medical schools with their hospitals, there are fourteen hospitals in San Francisco. These include the San Francisco Hospital, which is in reality a group of hospitals with its divisions: the Emergency Hospitals; the Psychiatric Department; the Tuberculosis Division; and the Laguna Honda Home, a hospital for elderly and chronically ill patients.

The famous cyclotron of the University of California is located in Berkeley and is operated in connection with the Physics Department located on that campus. A sizeable department of medical physics has developed in connection with the cyclotron and is located on the Berkeley campus. Also, a medical clinic has been developed in this connection, owing to the necessity of accommodating the patients who apply for various types of treatment with radioactive agents. These radioactive agents are also available and are utilized in the regular clinics at the Medical School in San Francisco. The Laboratory of Experimental Oncology was established at the Laguna Honda Home in January of 1947. It is a joint project of the National Cancer Institute, National Institute of Health, United States Public Health Service, Department of Public Health of the City and County of San Francisco and the University of California Medical School. This laboratory contains electrophysiologic equipment for the study of physiology in cancer patients, a biochemical-immunologic unit, and also a ward of 25 beds.

In addition to being the leading medical center on the Pacific Coast, San Francisco is famous for its beauty as a city and for its interesting environment. Situated by the Golden Gate and possessing two world-famous bridges, it has mountain scenery close at hand in Marin County across the Golden Gate Bridge. The redwoods of Muir Woods are near-by. The Valley of the Moon and the Spanish Missions are readily accessible by automobile. It is interesting to contemplate that, with improved air-travel facilities, it is possible to leave San Francisco in the morning and have dinner in the evening in the Hawaiian Islands. The Yosemite Valley is beautiful in the latter part of the month of April but is apt to be cool, particularly at night.

With the abundant opportunities for sight-seeing and entertainment and with the available facilities of our hospitals and medical schools, it is our hope and expectation that the 29th Annual Session of the College will prove of exceptional interest and satisfaction to the members and guests when they assemble here in San Francisco during the coming month of April.

GENERAL INFORMATION

GENERAL HEADQUARTERS

Civic Auditorium

Grove Street

Registration headquarters, information bureau, technical exhibits, general sessions, morning lectures, panel discussions, meetings of Board of Regents, Board of Governors and committees. Panel discussions will also be scheduled in the Third Floor Hall, Public Health Building, 101 Grove Street. The Annual Convocation and Banquet will take place in the Fairmont Hotel, 950 Mason Street.

HOTEL ACCOMMODATIONS

Ample accommodations have been allocated for the housing of members of the College and guests during the 1948 Annual Session. San Francisco, however, has no large hotels of the metropolitan type, but has many fine smaller hotels. Very few single rooms are available; members are urged to use double rooms. The hotels named below have officially promised accommodations, and will honor requests for reservations sent in directly by members and guests. The absence of quoted rates for single rooms indicates the hotel has guaranteed no single rooms. The various classes, A, B and C, in many instances indicate only comparison in size, for many Class B hotels are comparable with Class A hotels, although smaller. In requesting reservations, please state clearly date and time of anticipated arrival and departure; mention the fact that reservations are being made in connection with the Annual Session of The American College of Physicians; and enclose a check for \$5.00 as deposit.

Officers, Regents, Governors, Speakers and Clinicians on the Program should address their requirements to Mr. E. R. Loveland, Executive Secretary, The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., who has reserved for this group adequate accommodations in the Mark Hopkins and Fairmont Hotels.

The Whitcomb Hotel, 1231 Market Street, will be the official headquarters of the technical exhibitors, who may make their reservations direct by communication with Mr. Charles Knapp, Manager.

OFFICIAL HOTELS

CLASS A RATING

CLIFT—Geary & Taylor Sts. †152
 Double—\$7.00, \$8.00, \$9.00
 Twin—\$8.00, \$10.00, \$12.00
 Suites—\$20.00, \$25.00, \$30.00

PALACE—Market & New Montgomery Sts. †330
 Double—\$8.00, \$9.00, \$11.00
 Twin—\$9.00, \$10.00, \$12.00
 Suites—\$18.00 to \$35.00
 Roll-away bed in any room, add \$2.00

ST. FRANCIS—Union Square. †400
 Double—\$8.00, \$9.50
 Twin—\$8.00, \$9.50, \$10.50, \$12.00, \$14.00
 Two rooms, bath between—\$18.00, \$20.00
 Each extra person, \$2.50 a day

SIR FRANCIS DRAKE—450 Powell St. †375
 Single—\$6.00, \$7.00, \$8.00
 Double—\$8.00, \$9.00, \$10.00
 Twin—\$9.00, \$10.00, \$11.00
 Each extra person, \$2.00 a day

CLASS B RATING

BELLEVUE—Geary & Taylor Sts. †80
 Double—\$6.00
 Twin—\$6.50
 Suites—\$10.00

CALIFORNIAN—405 Taylor St. †118
 Single—\$3.00
 Double—\$5.25
 Twin—\$6.00
 Suites—\$12.00 (up to 4 persons)

CANTERBURY—750 Sutter St. †50
 Double—\$5.00, \$6.00
 Twin—\$6.00, \$6.50, \$7.00
 Each extra person, \$1.00 a day

CHANCELLOR—433 Powell St. †80
 Double—\$5.00
 Twin—\$6.00
 Each extra person, \$1.00 a day

DRAKE-WILTSHIRE—340 Stockton St. †190
 Single—\$2.50, \$3.00
 Double—\$4.00, \$4.50, \$5.00
 Twin \$6.00
 Each extra person, \$1.50

EMBASSY—610 Polk St. †24
 Double—\$4.00
 Twin—\$4.00
 Each extra person, \$1.50 a day

MANX—225 Powell St. †95
 Single—\$3.00, \$3.50
 Double—\$4.00, \$4.50
 Twin—\$5.00, \$6.00

MAURICE—761 Post St. †22
 Double—\$5.00
 Twin—\$6.00
 Suites—\$10.00

PLAZA—Post at Stockton Sts. †40
 Double—\$5.00 to \$6.00
 Twin—\$6.50 to \$8.50

STEWART—351 Geary St. †100
 Double—\$4.00, \$4.50
 Twin—\$4.50, \$5.00
 Suites—\$8.00

CLASS C RATING

BALDWIN—321 Grant Ave. †22
 Double—\$4.00
 Twin—\$5.50

BARCLAY—235 O'Farrell St. †9
 Single—\$2.50
 Double—\$3.00
 Twin—\$3.50

BRAYTON—50 Turk St. †54
 Double—\$3.00*, \$3.50, \$4.00
 Twin—\$5.00
 Two rooms, bath between—\$6.50, \$7.00, \$8.00
 Each extra person, \$1.00 per day

CARLTON—1075 Sutter St. †20
 Double—\$3.50
 Twin \$4.00
 Each extra person, \$1.25 a day

† Gross number of accommodations (persons) guaranteed.

* Indicates without bath; otherwise, all rooms with private bath.

† Gross number of accommodations (persons) guaranteed.

CARTWRIGHT—524 Sutter St. †50 Double—\$4.00 Twin—\$4.50 Each extra person, \$1.00 a day	LOMBARD—1015 Geary St. †50 Double—\$5.00 Twin—\$6.50
COLUMBIA—411 O'Farrell St. †30 Double or Twin—\$3.50	NEW ALDEN—333 Fulton St. †15 Double—\$2.50, \$3.00, \$3.50 Room with 1 double and 1 single bed—\$4.00 Room with 2 double beds—\$4.50
COMMODORE—825 Sutter St. †50 Double—\$6.00 Twin—\$7.00	OLYMPIC—230 Eddy St. †60 Double—\$4.00 to \$5.00 Twin—\$4.50 to \$5.50
DEVONSHIRE—335 Stockton St. †25 Single—\$2.50* Double—\$3.00*, \$3.50, \$4.50 Twin—\$3.50*, \$4.50, \$5.00 Two rooms, bath between—\$8.00 Suites—\$12.00	PICKWICK—5th & Mission Sts. †120 Double—\$4.00, \$4.50, \$5.00 Twin—\$4.50, \$5.00, \$5.50 Each extra person, \$1.00 a day
EL CORTEZ—550 Geary St. †50 Single—\$3.50, \$4.00, \$5.00 Double—\$4.50, \$5.00, \$6.00 Twin—\$6.00, \$7.00 Each extra person, \$1.00 a day	POWELL—17 Powell St. †58 Double—\$4.00 Each extra person, \$1.00 a day
FEDERAL—1087 Market St. †57 Double—\$2.50*, \$3.50 Twin—\$3.00*, \$4.50 Two rooms, bath between—\$6.50 to \$7.00	ROOSEVELT—240 Jones St. †45 Single—\$3.00, \$3.50 Double—\$3.50, \$4.00 Each extra person, \$1.00 a day
FIELDING—Geary & Mason Sts. †40 Double—\$5.00 Twin—\$6.00	SENATE—467 Turk St. †45 Double—\$3.00 Each extra person, \$1.00 a day
GOLDEN STATE—114 Powell St. †80 Double—\$2.50*, \$3.50 Twin—\$5.00 Two rooms, bath between—\$6.00 Each extra person, \$1.50 a day	SENATOR—519 Ellis St. †24 Double—\$3.00 Twin—\$4.00
HERBERT—161 Powell St. †90 Double—\$2.00 to \$3.50*, \$3.50 to \$5.00 Roll-away bed in any room, add \$1.50	SHAW—Market & McAllister Sts. †65 Single—\$3.50 Double—\$5.00 Twin—\$6.00 Each extra person, \$1.50 a day
KEYSTONE—54 Fourth St. †33 Single—\$3.00 Double—\$3.50 Twin—\$5.00	SUTTER—Sutter & Kearney Sts. †50 Double—\$5.00 Twin—\$6.00
LANKERSHIM—55 Fifth St. †100 Double—\$2.50*, \$3.50	WASHINGTON—Grant Ave. & Bush St. †40 Double—\$4.00, \$4.50, \$5.00 Twin—\$4.50, \$5.00, \$5.50

† Gross number of accommodations (persons) guaranteed.

* Indicates without bath; otherwise, all rooms with private bath.

† Gross number of accommodations (persons) guaranteed.

Who May Register—

- (a) All members of The American College of Physicians in good standing for 1948.
- (b) All newly elected members.
- (c) Senior and graduate medical students pursuing courses at the University of California and Leland Stanford Junior University, without registration fee, *upon presentation of matriculation cards or other evidence of registration at these institutions*; exhibits, general sessions and morning lectures.
- (d) Members of the staff, including internes, of the hospitals participating in the program, without registration fee, *upon presentation of proper identification*; exhibits, general sessions and morning lectures.
- (e) Members of the Medical Corps of the Army, Navy and Public Health Services of the United States and Canada, without registration fee, *upon presentation of proper credentials*.
- (f) Qualified physicians who may wish to attend this Session as visitors; such physicians shall pay a registration fee of \$12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published) included within such fee.

Registration Bureau—While official registration will start on Monday morning, April 19, advance registration of members and exhibitors will be provided for within the main entrance of the Civic Auditorium on Sunday, April 18, from 2:30 to 5:00 in the afternoon. The Registration Bureau will be open through the week from 8:30 A.M. to 5:45 P.M.

Registration Blanks for All Clinics and Panel Discussions will be sent with the final program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

Bulletin Boards for special announcements will be located near the Registration Bureau in the Civic Auditorium.

Transportation—Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the Meeting.

The General Business Meeting of the College will be held at 2:00 P.M., Thursday, April 22, immediately preceding the afternoon scientific session. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors and the annual reports will be received from the Secretary-General, Executive Secretary and Treasurer. The President-Elect, Dr. Walter W. Palmer, New York, N. Y., will be inducted into office.

Board and Committee Meetings—The following meetings are scheduled as indicated. With the exception of the dinner meeting (following paragraph) all meetings will be held in the Civic Auditorium. Special meetings will be announced and posted.

A dinner meeting of the Board of Regents and of the Board of Governors will be held at the Mark Hopkins Hotel, Sunday, April 18, at 7:00 P.M.

COMMITTEE ON CREDENTIALS

Saturday, April 17, 2:00 P.M., Room 108, 1st Floor

ADVISORY COMMITTEE ON POSTGRADUATE COURSES

Sunday, April 18, 9:30 A.M., Room 203, 2nd Floor

COMMITTEE ON FINANCE

Monday, April 19, 10:30 A.M., Room 108, 1st Floor

COMMITTEE ON PUBLIC RELATIONS

Monday, April 19, 11:30 A.M., Room 108, 1st Floor

**JOINT MEETING: BOARD OF REGENTS AND
BOARD OF GOVERNORS**

Sunday, April 18, 2:00 P.M., Room 203, 2nd Floor

BOARD OF REGENTS

Tuesday, April 20, 12:00 M., Room 203, 2nd Floor*

Friday, April 23, 12:00 M., Room 203, 2nd Floor*

BOARD OF GOVERNORS

Wednesday, April 21, 12:00 M., Room 203, 2nd Floor*

SPECIAL TRAINS AND POST-CONVENTION TOURS

For the convenience of members and guests of the College, arrangements have been made with the Baltimore and Ohio, Burlington Route, Denver Rio Grande, Missouri Pacific, Western Pacific and Santa Fe Railroads for three special trains to and from the San Francisco Annual Session. Train No. 1, departing from New York on Wednesday, April 14, will serve those in the New England, Middle Atlantic and South Atlantic States as well as Eastern Ohio. Train No. 2, operated for the convenience of members in Eastern and Central Canada, Western New York, Michigan, Northwestern Ohio and Indiana, Illinois, Wisconsin, Minnesota and Iowa, will depart from Chicago Thursday morning, April 15. Train No. 3, serving the South and Southwest as well as West Virginia, Ohio, Indiana, Missouri, Kansas and Oklahoma, will leave Cincinnati Thursday morning, April 15, and proceed via St. Louis to Colorado Springs, at which point the three special trains converge, on Friday, April 16. Stops for sight-seeing will be made in that city and in Salt Lake City. The three special trains proceed from Colorado Springs to San Francisco on a common schedule, arriving Sunday evening, April 18.

Members not served directly by these schedules are urged, whenever possible, to arrange their itineraries so that they may join one of the special trains at the most convenient point.

The special trains will leave San Francisco on Friday evening, April 23. There will be sight-seeing stops at the Yosemite Valley and at Los Angeles (where local members will have a program of entertainment and inspection for the two and a half days available). Stops will also be made at the Grand Canyon in Arizona and the Carlsbad Caverns, New Mexico. The three special trains will operate on the same schedule to Kansas City, Mo., at which point they will separate. Train No. 1 will

* Buffet Luncheon served.

arrive in New York Sunday morning, May 2. Train No. 2 will arrive in Chicago Saturday morning, May 1. Train No. 3 will arrive in St. Louis the morning of Saturday, May 1, and Cincinnati the evening of that same day.

The cooperating railroads have published a special bulletin of the official itinerary, which includes information concerning schedules, rates, accommodations and special features. This bulletin will be mailed with the final program to all members of the College; others may obtain copies of the bulletin by addressing Mr. W. P. Cox, Baltimore & Ohio R. R., Broad and Walnut Sts., Philadelphia 9, Pa., through whom all accommodations on these special trains will be reserved.

POST-CONVENTION AIR CRUISE TO THE HAWAIIAN ISLANDS

For those who wish to visit Hawaii after the Annual Session, two all-expense air cruises from San Francisco have been planned. Both will leave by Pan American Clipper on Saturday morning, April 24. One cruise will occupy seven days, with return to San Francisco on Saturday, May 1; the other, ten days, returning to San Francisco on Tuesday, May 4.

Full information concerning these cruises is contained in the special trains bulletin referred to in the section above.

TO HAWAII BY SHIP

Many members of the College have indicated their interest in a cruise to Hawaii by water, either one or both ways. However, at the time of publication, no information had been received on the basis of which adequate steamship service could be predicted or guaranteed. It is possible that adequate ship accommodations may be established by the Matson Line by the time of the Annual Session. Information on this point may also be secured from Mr. Cox.

SPECIAL FEATURES

Monday, April 19, 1948

The Entertainment Committee has arranged for a concert by the **San Francisco Symphony Orchestra** under the direction of the celebrated conductor, Pierre Monteux, who has arranged a program which should have a wide appeal. The concert will begin at 8:15 P.M., in the auditorium of the Veterans' Memorial Building on Van Ness Avenue. Tickets may be obtained only at the Registration Bureau on Monday, April 19, and will be limited to Fellows and Associates of the College. No more than two tickets can be issued to a Fellow or Associate; two tickets may be issued to those accompanied by a member of the family. No reservations can be made in advance, and tickets will be available on the basis of first come, first served.

Wednesday, April 21, 1948

THE ANNUAL CONVOCATION OF THE COLLEGE—8:30 P.M., Ballroom, Fairmont Hotel. All members of the College and their families, and those of the public who are interested, are invited. All physicians elected Fellows of the College since the 1947 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents, Governors and new Fellows to be inducted, are requested to assemble in the Ballroom Annex, Fairmont Hotel, at 7:45 P.M., preparatory to the formation of the procession. They will be

conducted to their seats by the Marshal of the Convocation, Dr. T. Grier Miller, promptly at 8:30 P.M. It is suggested that all appear in evening clothes.

The Convocation ceremony will include the President's address and a Convocational Oration, "The Golden Gate of Medicine," by Dr. Alan Gregg, Director of the Medical Sciences of The Rockefeller Foundation, New York, N. Y. The John Phillips Memorial Medal for 1948, the James D. Bruce Memorial Medal for 1948, and the Alfred Stengel Diploma for 1948, will be awarded. The recipients of Research Fellowships of the College for 1948 will be announced. Also, Masterships will be conferred upon five outstanding Fellows of the College. The newly elected Fellows will be presented by the Secretary-General, Dr. George Morris Piersol, and, after subscribing to the Fellowship Pledge, will be inducted by the President. Following the Convocation, after a brief intermission during which guests will retire to the Lobby while the Ballroom is cleared, the President's Reception and Dance will take place in the Ballroom. All members and guests are requested to pass along the receiving line.

Thursday, April 22, 1948

A SPECIAL CEREMONY has been arranged to honor the memory of Robert Louis Stevenson whose residence in California had a beneficial influence on California Life. At 5:30 P.M., a brief ceremony will be held at the Stevenson Monument in Portsmouth Square. Mr. Joseph R. Knowland, Chairman of the State Park Commission, will make a few appropriate remarks. President Hugh J. Morgan will lay a wreath on the monument and speak briefly in tribute to the memory of one who, although he had occasion to encounter many physicians during his long period of disability, could still speak of the physician in the most commendatory manner.

THE ANNUAL BANQUET will be held in the Ballroom of the Fairmont Hotel at 8:00 P.M. Professor Frederick C. Woellner, Dean of the School of Education of the University of California at Los Angeles, will be the speaker of the evening on the subject, "A Philosophy of Trouble." Dr. William J. Kerr will be the Toastmaster.

All members of the College, physicians of San Francisco and surrounding area, visitors attending the Session, guests and friends, with their families, are cordially invited. Table reservations for groups may be arranged. Orchestral music will be furnished, and the evening has been planned as a most delightful occasion. Tickets should be purchased at the Registration Bureau by Wednesday afternoon, so that adequate preparations can be consummated.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The Ladies' Entertainment Committee has prepared a program which, it hopes, will be interesting and enjoyable to all. The guests are requested to register at the Ladies' Headquarters in the Lobby of the Mark Hopkins Hotel on their arrival in San Francisco. Registration will start on Sunday afternoon, April 18, and continue each day thereafter through April 22.

Tickets for the various entertainment features will be procurable at the time of registration and, as accommodations at some of these are limited, early registration is advisable.

Programs will be available at the time of registration and the Committee will be prepared to offer maps and lists of theaters, shops, restaurants and places of interest in and about San Francisco.

Monday, April 19, 1948

9:00 A.M. to 4:00 P.M.: Registration, Lobby, Mark Hopkins Hotel.

Afternoon: 3:00 to 5:00. Welcoming Tea, Fairmont Hotel.

Evening: 8:15. San Francisco Symphony Orchestra. (See under Special Features for Monday.)

Tuesday, April 20, 1948

9:00 A.M. to 4:00 P.M.: Registration, Lobby, Mark Hopkins Hotel.

Morning: 9:30 to 1:30 P.M. San Francisco Bay Cruise. Buses to leave the Mark Hopkins Hotel at 9:30 and to return to the hotel at 1:30 P.M. Price of cruise, including bus fare from and to the hotel, \$2.60. Light luncheon may be had on board at extra cost, if desired.

Wednesday, April 21, 1948

9:30 A.M. to 4:00 P.M.: Registration, Lobby, Mark Hopkins Hotel.

Afternoon: 12:00 to 2:00. Luncheon and Fashion Show at the Palace Hotel. Price, \$3.00.

Evening: 8:30. Convocation and President's Reception and Dance, Ballroom, Fairmont Hotel.

Thursday, April 22, 1948

9:30 A.M. to 4:00 P.M.: Registration, Lobby, Mark Hopkins Hotel.

Afternoon: Bus tour of San Francisco and Tea at the St. Francis Yacht Club. Buses to leave the Mark Hopkins Hotel at 1:00, arriving at the St. Francis Yacht Club for tea at 4:00, and returning to the hotel at 5:00. Those desiring to attend the Stevenson Ceremony in Portsmouth Square at 5:30 P.M., before returning to the hotel, should sign up with Mrs. LeRoy H. Briggs at the Registration Desk. Price of Tour, including Tea, \$3.75.

Evening: 8:00. Annual Banquet of The College, Ballroom, Fairmont Hotel.

On Tuesday and Wednesday afternoons, conducted tours of Gump's and Chinatown will be arranged, if desired. Register with Mrs. LeRoy H. Briggs at Registration Desk.

Arrangements have been made for any members so desiring to play golf at the San Francisco Golf Club on Tuesday, April 20. Green fees, \$2.00 a person. Transportation will be furnished. To make arrangements, call Mrs. George S. Johnson, Fillmore 6-6700, or apply at Registration Desk.

THE TECHNICAL EXHIBIT

The Technical Exhibit will be located in the Arena, ground floor of the Civic Auditorium.

The Committee on Exhibits of the College maintains highest possible standards in the conduct of this Exhibit. Exhibitors are admitted only by invitation; irrelevant

products are eliminated, and only firms which present a group of approved products of scientific interest to the internist and allied specialists may exhibit. Questionable methods of selling are prohibited.

The exhibitor's aim is to announce new products and to present new and interesting information to members and guests of the College. Likewise, many exhibitors take advantage of this opportunity to give aid and service directions to members who have previously adopted their products. Furthermore, this Exhibit provides the only convenient and direct method of contacting, personally, members of the College.

Members and guests of the College are encouraged to accord the exhibitors courteous and interested attention, thus recognizing their contributions to the Meeting and the effort that they make and the expense to which they go in building superior displays and furnishing, freely, valuable information.

The Technical Exhibit will be open during the following hours:

Monday, April 19.....	8:30 A.M. to 5:45 P.M.
Tuesday, April 20.....	10:30 A.M. to 5:45 P.M.
Wednesday, April 21.....	8:30 A.M. to 5:45 P.M.
Thursday, April 22.....	10:30 A.M. to 5:45 P.M.
Friday, April 23.....	8:30 A.M. to 2:45 P.M.

Special intermissions have been arranged, providing additional time for the inspection of the exhibits.

1948 EXHIBITORS

Abbott Laboratories, North Chicago, Ill.
 American Association of University Presses
 Ames Company, Inc., Elkhart, Ind.
 Armour Laboratories, The, Chicago, Ill.
 Ayerst, McKenna & Harrison, Limited, New York, N. Y.
 Becton, Dickinson & Co., Rutherford, N. J.
 Bilhuber-Knoll Corp., Orange, N. J.
 Blakiston Company, The, Philadelphia, Pa.
 Bristol Laboratories, Inc., New York, N. Y.
 Burdick Corporation, The, Milton, Wis.
 Burroughs Wellcome & Co. (U.S.A.), Inc., Tuckahoe, N. Y.
 Cambridge Instrument Co., Inc., New York, N. Y.
 Cameron Surgical Specialty Company, Chicago and New York
 Camp & Company, S. H., Jackson, Mich.
 Carnation Company, Oconomowoc, Wis.
 Ciba Pharmaceutical Products, Inc., Summit, N. J.
 Collins, Inc., Warren E., Boston, Mass.
 Commercial Solvents Corp., New York, N. Y.
 Cutter Laboratories, Berkeley, Calif.
 Davies, Rose & Company, Limited, Boston, Mass.
 Davis Company, F. A., Philadelphia, Pa.
 Devereux Schools, Devon, Pa., and Santa Barbara, Calif.
 Doak Company, Inc., Cleveland, Ohio
 Doho Chemical Corporation, The, New York, N. Y.
 Electro-Physical Laboratories, Inc., New York, N. Y.
 Fleet Company, Inc., C. B., Lynchburg, Va.
 General Electric X-Ray Corporation, Milwaukee, Wis.

Gerber Products Company, Fremont, Mich.
Grune & Stratton, Inc., New York, N. Y.
Harrower Laboratories, Inc., The, Glendale, Calif.
Heinz Co., H. J., Pittsburgh, Pa.
Hoeber, Inc., Paul B., New York, N. Y.
Hoffmann-LaRoche, Inc., Nutley, N. J.
Hollister-Stier Laboratories, Spokane, Wash.
Hygeia Nursing Bottle Co., Inc., The, Buffalo, N. Y.
Jones Metabolism Equipment Co., Chicago, Ill.
Kalak Water Co. of New York, Inc., New York, N. Y.
Lea & Febiger, Philadelphia, Pa.
Lederle Laboratories, Inc., Pearl River, N. Y.
Lilly and Company, Eli, Indianapolis, Ind.
Lippincott Company, J. B., Philadelphia, Pa.
Macmillan Company, The, New York, N. Y.
Maltine Company, The, New York, N. Y.
Mead Johnson & Company, Evansville, Ind.
Medical Bureau, The, Chicago, Ill.
Medical Film Guild, New York, N. Y.
Medical Protective Company, The, Fort Wayne, Ind.
Merck & Co., Inc., Rahway, N. J.
Merrell Company, The Wm. S., Cincinnati, Ohio
Mosby Company, The C. V., St. Louis, Mo.
Parke, Davis & Company, Detroit, Mich.
Picker X-Ray Corporation, New York, N. Y.
Pitman-Moore Company, Indianapolis, Ind.
Procter & Gamble Company, The, Cincinnati, Ohio
Reed & Carnrick, Jersey City, N. J.
Sanborn Company, Cambridge, Mass.
Sandoz Chemical Works, Inc., New York, N. Y.
Saunders Company, W. B., Philadelphia, Pa.
Schenley Laboratories, Inc., New York, N. Y.
Schering Corporation, Bloomfield, N. J.
Searle & Co., G. D., Chicago, Ill.
Sharp & Dohme, Incorporated, Philadelphia, Pa.
Smith-Dorsey Company, The, Lincoln, Nebr.
Smith, Kline & French Laboratories, Philadelphia, Pa.
Squibb & Sons, E. R., New York, N. Y.
Stacey, Inc., J. W., San Francisco, Calif.
Technicon Company, The, New York, N. Y.
Upjohn Company, The, Kalamazoo, Mich.
U. S. Vitamin Corporation, New York, N. Y.
Varick Pharmacal Company, Inc., New York, N. Y.
Warner & Co., Inc., William R., New York, N. Y.
Westwood Pharmacal Corp., Buffalo, N. Y.
Whirlpool Carriage, Inc., Westport, Conn.
White Laboratories, Inc., Newark, N. J.
Winthrop-Stearns Inc., New York, N. Y.
Wyeth Incorporated, Philadelphia, Pa.
Year Book Publishers, Inc., The, Chicago, Ill.

OUTLINE OF THE SAN FRANCISCO SESSION

Civic Auditorium events and rooms are indicated in bold type

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	April 19	April 20	April 21	April 22	April 23
9:00 A.M. to 11:30 A.M.	Morning free. Registration, Exhibits, etc. (Arena)	Hospital Clinics	Morning Lectures* (Polk & Larkin Halls) 9:30-11:30	Hospital Clinics	Morning Lectures* (Polk & Larkin Halls) 9:30-11:30
12:00 M. to 1:15 P.M.		Panel Discussions (Polk, Larkin, Rm. 403) (also Health Bldg.)	Panel Discussions (Polk, Larkin, Rm. 403) (also Health Bldg.)	Panel Discussions (Polk, Larkin, Rm. 403) (also Health Bldg.)	Panel Discussions (Polk, Larkin, Rm. 403) (also Health Bldg.)
2:00 P.M. to 5:25 P.M.	1st General Session (Polk Hall)	2nd General Session (Polk Hall)	3rd General Session (Polk Hall)	Annual Business Meeting 4th General Session (Polk Hall)	5th General Session (Polk Hall)
8:00 P.M. to 11:00 P.M.	San Francisco Symphony Concert		Convocation, followed by President's Reception (Ballroom, Fairmont Hotel)	Annual Banquet (Ballroom, Fairmont Hotel)	

* Two simultaneous series.

Note: Exhibits will be open on Monday and Wednesday from 8:30 A.M. to 5:45 P.M.; on Tuesday and Thursday, from 10:30 A.M. to 5:45 P.M.; on Friday, from 8:30 A.M. to 2:45 P.M.

GENERAL SESSIONS PROGRAM

Polk Hall, Civic Auditorium

FIRST GENERAL SESSION

Monday Afternoon, April 19, 1948

General Chairmen, William J. Kerr, F.A.C.P., and Ernest H. Falconer, F.A.C.P.
Dr. Kerr presiding

P.M.

2:00 Invocation:

Reverend HARLEY H. GILL, D.D., Superintendent of Northern California Congregational Conference.

Addresses of Welcome:

The Honorable ELMER E. ROBINSON, Mayor of San Francisco.

J. C. GEIGER, F.A.C.P., Director of Public Health.

ROBERTSON WARD, F.A.C.S., President of the San Francisco County Medical Society.

WILLIAM G. DONALD, President of the Alameda County Medical Society.

JOHN W. CLINE, F.A.C.S., President of the California Medical Association.

LOREN R. CHANDLER, F.A.C.S., Dean, Stanford University School of Medicine.

F. SCOTT SMYTH, F.A.A.P., Dean, University of California Medical School.

Response to Addresses of Welcome:

HUGH J. MORGAN, F.A.C.P., President of The American College of Physicians.

President Hugh J. Morgan, F.A.C.P., presiding

2:30 The James D. Bruce Lecture on Preventive Medicine: The Challenge of Preventive Medicine.

JAMES STEVENS SIMMONS, F.A.C.P., Brigadier General, (MC), U.S.A., Ret., Dean and Professor of Public Health, The Harvard School of Public Health, Boston, Mass.

3:15 INTERMISSION.

3:35 Revisions in the Concept of Disease.

KARL A. MENNINGER (by invitation), Manager, Winter Veterans Administration Hospital; General Director, Department of Education, The Menninger Foundation; Topeka, Kans.

3:55 The Alarm Reaction and the Diseases of Adaptation.

HANS SELYE (by invitation), Professor and Director of the Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal, Montreal, P.Q., Can.

4:15 Hypertension as a Reaction to Situational Threats: Experimental Study of Variations in Blood Pressure and Renal Blood Flow.

STEWART G. WOLF, JR. (by invitation), Assistant Professor of Medicine, Cornell University Medical College; Assistant Attending Physician, The New York Hospital; New York, N. Y.

4:35 Psychotherapeutic Blunders.

HENRY M. THOMAS, JR., F.A.C.P., Associate Professor of Medicine, Johns Hopkins University School of Medicine; Visiting Physician, Johns Hopkins Hospital; Baltimore, Md.

4:55 The Newer Analgesic Drugs: Their Use and Abuse.

HARRIS ISBELL (Associate), Director of Research, U. S. Public Health Service Hospital, Lexington, Ky.

5:15 ADJOURNMENT.

Monday Evening

PROGRAM OF ENTERTAINMENT

Arranged by the San Francisco Committee

Consult announcement concerning Special Features,
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SECOND GENERAL SESSION

Tuesday Afternoon, April 20, 1948

Polk Hall, Civic Auditorium

Presiding Officer

Walter W. Palmer, F.A.C.P., New York, N. Y.

P.M.

2:00 Skeletal Lesions in Hodgkin's Disease.

ERNEST H. FALCONER, F.A.C.P., Clinical Professor of Medicine, Chief of Hematologic Clinic, University of California Medical School, San Francisco, Calif.

2:20 Observations on Relapses in Pernicious Anemia.

EDGAR JONES, F.A.C.P., Associate Professor of Clinical Medicine, Vanderbilt University School of Medicine; Associate Visiting Physician, Vanderbilt University Hospital; Nashville, Tenn.

2:40 Radioactive Isotopes in Medicine.

JOHN H. LAWRENCE (by invitation), Chairman, Division of Medical Physics, University of California, Berkeley, Calif.

3:00 The Medical Aspects of Radiation Sickness.

STAFFORD L. WARREN (by invitation), Dean and Professor of Biophysics, University of California at Los Angeles School of Medicine, Los Angeles, Calif.

3:20 INTERMISSION.**3:40 Water Balance in Heart and Kidney Disease.**

F. R. SCHEMM, F.A.C.P., Head of the Department of Internal Medicine, Great Falls Clinic, Great Falls, Mont.

4:00 Therapeutic Use of Sodium, Potassium, and Phosphorus Solutions in Medical Emergencies.

GEORGE W. THORN, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School; Physician-in-Chief, Peter Bent Brigham Hospital; Boston, Mass.

4:20 Fat Absorption in the Digestive Tract and the Use of Surface Acting Agents.

CHESTER M. JONES, F.A.C.P., Clinical Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital; Boston, Mass.

4:40 Prevention of Recurrences in Peptic Ulcer.

THEODOR L. ALTHAUSEN, F.A.C.P., Professor of Medicine and Chief of Gastro-intestinal Clinic, University of California Medical School, San Francisco, Calif.

5:00 ADJOURNMENT.

THIRD GENERAL SESSION

Wednesday Afternoon, April 21, 1948

Polk Hall, Civic Auditorium

Presiding Officer

Reginald Fitz, F.A.C.P., Boston, Mass.

P.M.

2:00 The John Phillips Memorial Lecture: The Intracellular Environment for Infectious Agents.

ERNEST W. GOODPASTURE (by invitation), Professor of Pathology and Dean, Vanderbilt University School of Medicine, Nashville, Tenn.

2:45 Bacterial Resistance to Antibiotics.

C. PHILLIP MILLER, F.A.C.P., Professor of Medicine, University of Chicago, Chicago, Ill.

3:05 INTERMISSION.

3:25 Present Position of Our Knowledge of Anterior Pituitary Hormones.

HERBERT M. EVANS (by invitation), Director, Institute of Experimental Biology, University of California, Berkeley, Calif.

3:45 Diagnostic Significance of Hormones Excreted in the Urine.

ROBERTO F. ESCAMILLA, F.A.C.P., Associate Clinical Professor of Medicine, University of California Medical School, San Francisco, Calif.

4:05 The Differential Diagnosis of the Symptom Amenorrhea.

HANS LISSER, F.A.C.P., Clinical Professor of Medicine, University of California Medical School; Chief of D-Unit, University of California Hospital Out-patient Department; Chief of Service, Endocrinology and Diabetes, Franklin Hospital; San Francisco, Calif.

4:25 Radioiodine and Graves' Disease.

MAYO H. SOLEY (by invitation), Professor of Medicine, University of California Medical School; Associate Visiting Physician, University of California Hospital; San Francisco, Calif.

4:45 Use of Estrogens in Medicine.

ELMER L. SEVRINGHAUS, F.A.C.P., Consultant in Endocrinology, Gouverneur Hospital, New York, N. Y., and Hospital of St. Barnabas and for Women and Children, Newark, N. J. (Montclair, N. J.).

5:05 Androgen Therapy.

WILLARD O. THOMPSON, F.A.C.P., Clinical Professor of Medicine, University of Illinois College of Medicine; Attending Physician, Grant and Henrotin Hospitals; Chicago, Ill.

5:25 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, April 21, 1948

8:30 o'Clock

Ballroom, Fairmont Hotel

T. GRIER MILLER, Marshal

All members of the profession and the general public are cordially invited. No admission tickets required.

1. Invocation.

The Right Reverend KARL MORGAN BLOCK, D. D., Bishop of California Protestant Episcopal Church.

2. The President's Address: "Professio."

HUGH J. MORGAN.

3. Presentation of Newly Elected Fellows and Recital of the Pledge.

GEORGE MORRIS PIERSOL, Secretary-General.

4. Presentation of Newly Elected Masters.**5. Presentation of the John Phillips Memorial Medal for 1948.****6. Presentation of the James D. Bruce Memorial Medal for 1948.****7. Presentation of the Alfred Stengel Memorial Award for 1948.****8. Announcement of Research Fellows for 1948-49.****9. Convocational Oration: "The Golden Gate of Medicine."**

ALAN GREGG, Director of the Medical Sciences of The Rockefeller Foundation. New York, N. Y.

PRESIDENT'S RECEPTION

The President's Reception and Dance will follow one-half hour after this program, time being required to re-set the ballroom. A cordial invitation is extended to all members and guests, with their families.

FOURTH GENERAL SESSION

Thursday Afternoon, April 22, 1948

Polk Hall, Civic Auditorium

P.M.

2:00 THE ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Reports will be received from the Secretary-General, Executive Secretary and the Treasurer; elections of new Officers, Regents and Governors will take place; President-Elect Walter W. Palmer, of New York, N. Y., will be inducted as President and will make a brief inaugural address.

Presiding Officer

Francis G. Blake, F.A.C.P., New Haven, Conn.

2:40 The Physiologic Effects of Physical Therapy.

GEORGE MORRIS PIERSOL, M.A.C.P., Vice Dean for Medicine and Professor of Medicine, Graduate School of Medicine, and Professor of Clinical Medicine, School of Medicine; Director, Center for Research and Instruction in Physical Medicine; University of Pennsylvania, Philadelphia, Pa.

3:00. INTERMISSION.

3:20 Infectious Arteritis.

WILLIAM S. MIDDLETON, F.A.C.P., Professor of Medicine and Dean of the Medical School, University of Wisconsin; Physician, State of Wisconsin General Hospital; Madison, Wis.

3:40 Streptomycin in the Treatment of Tuberculosis.

J. BURNS AMBERSON, F.A.C.P., Professor of Medicine, College of Physicians and Surgeons, Columbia University; Visiting Physician-in-Charge, Chest Service, Bellevue Hospital; New York, N. Y.

4:00 The Pathogenesis of Rheumatic Fever.

WILLIAM J. KERR, F.A.C.P., Professor of Medicine and Chairman of the Division of Medicine, University of California Medical School, San Francisco, Calif.

4:20 Pathogenesis of Coccidioidomycosis.

CHARLES E. SMITH (by invitation), Professor of Public Health and Preventive Medicine, Stanford University School of Medicine; Expert Consultant to The Surgeon General; San Francisco, Calif.

4:40 Empyema: Factors Involved in Recovery Following Local Penicillin Therapy.

WILLIAM S. TILLET (by invitation), Professor of Medicine and Chairman of Department, New York University College of Medicine; Director, Third Medical Division, Bellevue Hospital; New York, N. Y.

5:00 The Pathogenesis of Human Brucellosis with Respect to Prevention and Treatment.

WESLEY W. SPINK, F.A.C.P., Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minn.

5:20 ADJOURNMENT.

FIFTH GENERAL SESSION

Friday Afternoon, April 23, 1948

Polk Hall, Civic Auditorium

Presiding Officer

Walter L. Palmer, F.A.C.P., Chicago, Ill.

P.M.

2:00 Retrograde Arteriography in the Diagnosis of Cardiovascular Lesions.

NORMAN E. FREEMAN, F.A.C.S. (by invitation), Associate Clinical Professor of Surgery, University of California Medical School, San Francisco, Calif.

2:20 Results of Extensive Thoraco-lumbar Sympathectomy for Hypertension.

JAMES A. EVANS, F.A.C.P., Physician, Department of Medicine, Lahey Clinic, Boston, Mass.

2:40 The Hemodynamic Effects of Sympathectomy.

ROBERT W. WILKINS (by invitation), Associate Professor of Medicine, Boston University School of Medicine; Assistant Director, Evans Memorial and Massachusetts Memorial Hospitals; Boston, Mass.

3:00 Essential Familial Hypercholesterolemia.

CHARLES F. WILKINSON, JR. (by invitation), Assistant Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.

3:20 INTERMISSION.

3:40 Clinical Aspects of the Acute Episode in Coronary Disease.

HERMANN L. BLUMGART (by invitation), Professor of Medicine, Harvard Medical School; Physician-in-Chief, Beth Israel Hospital; Boston, Mass.

4:00 The Capillary Factor in Ischemic, Asphyxic and Anoxic Myocardial Injury.

GEORGE R. MENEELY, F.A.C.P., Assistant Professor of Medicine, Vanderbilt University School of Medicine; Director of the Heart Station, Vanderbilt University Hospital; Nashville, Tenn.

4:20 Coronary Artery Occlusion in Man and Animals Studied by Radioactive Isotopes.

MYRON PRINZMETAL (by invitation), Senior Attending Physician and Director of Beaumont Laboratory for Cardiovascular Disease, Cedars of Lebanon Hospital, Los Angeles, Calif.

4:40 The Use of the Anticoagulants in the Treatment of Diseases of the Heart and Blood Vessels.

IRVING S. WRIGHT, F.A.C.P., Associate Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, The New York Hospital; New York, N. Y.

5:00 ADJOURNMENT.

MORNING LECTURES

The Morning Lectures recognize the increasing interest in fundamental problems and are planned to supplement the subject matter of the General Sessions. The Lectures enable the speaker to cover his presentation fully and to utilize charts, slides, motion pictures and other media to amplify his presentation.

Morning Lectures will be offered on Wednesday and Friday mornings only; Hospital Clinics on Tuesday and Thursday mornings only. Two series of Morning Lectures will be presented concurrently in Polk and Larkin Halls, Civic Auditorium. The scheduling of the Lectures and the proximity of the two halls make it possible for an auditor to attend a part of each program if he so elects.

The Lectures will be open to all members and guests of the College.

Admission by regular registration badge; no special tickets.

Wednesday, April 21, 1948

Polk Hall, Civic Auditorium

Presiding Officer

Charles T. Stone, F.A.C.P., Galveston, Tex.

A.M.

9:30-10:20 The Animal Kingdom, a Reservoir of Disease.

KARL F. MEYER (by invitation), Director of the George Williams Hooper Foundation for Medical Research and Professor of Bacteriology, University of California, San Francisco, Calif.

10:20-10:40 INTERMISSION.

10:40-11:30 Problems in the Natural History of Poliomyelitis.

ALBERT B. SABIN (by invitation), Professor of Research Pediatrics, University of Cincinnati College of Medicine and The Children's Hospital Research Foundation, Cincinnati, Ohio

Larkin Hall, Civic Auditorium

Presiding Officer

William S. McCann, F.A.C.P., Rochester, N. Y.

- 9:30-10:20 **Experimental and Clinical Therapeutic Studies on Lymphosarcoma.**
C. P. RHODES, F.A.C.P., Director, Memorial Hospital and the Sloan-Kettering Institute for Cancer Research, New York, N. Y.
- 10:20-10:40 **INTERMISSION.**
- 10:40-11:30 **The Etiology and Management of the Hemorrhagic Diatheses.**
CHARLES A. DOAN, F.A.C.P., Professor of Medicine and Dean, College of Medicine; Director of Starling-Loving University Hospital; Director of Medical Research; The Ohio State University, Columbus, Ohio.

Friday, April 23, 1948

Polk Hall, Civic Auditorium

Presiding Officer

William D. Stroud, F.A.C.P., Philadelphia, Pa.

A.M.

- 9:30-10:20 **Our Changing Viewpoint on Congestive Failure.**
ISAAC STARR (by invitation), Professor of Therapeutic Research and Dean, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- 10:20-10:40 **INTERMISSION.**
- 10:40-11:30 **The Management of the Failing Heart.**
HARRY GOLD (by invitation), Professor of Clinical Pharmacology, Cornell University Medical College; Attending Physician-in-Charge of the Cardiovascular Research Unit, Beth Israel Hospital; Attending Cardiologist to Hospital for Joint Diseases; New York, N. Y.

Larkin Hall, Civic Auditorium

Presiding Officer

Maurice C. Pincoffs, M.A.C.P., Baltimore, Md.

- 9:30-10:20 **Syndromes of Abdominal Pain of Medical Origin Simulating Acute Surgical Conditions.**
ARTHUR L. BLOOMFIELD, F.A.C.P., Professor of Medicine, Stanford University School of Medicine, San Francisco, Calif.
- 10:20-10:40 **INTERMISSION.**
- 10:40-11:30 **The Prognosis and Treatment of Hepatic Insufficiency.**
CECIL JAMES WATSON, F.A.C.P., Professor of Medicine, University of Minnesota Medical School; Physician-in-Chief, University Hospitals; Minneapolis, Minn.

DEMONSTRATION TOURS**Wednesday, April 21, 1948****9:00 to 11:00 A.M.**

Buses with maximum capacity of 40 will leave Post Street entrance of St. Francis Hotel at 8:00 A.M. Buses are scheduled to return to the Auditorium by 12:00 noon. Cost of each tour, \$1.00. Reservations cannot be made in advance by mail, but tickets will be on sale (first come, first served) at the Clinic Ticket Desk at the Registration Headquarters at the Civic Auditorium.

- Tour 1.** **Demonstration at the Institute of Experimental Biology Laboratory, Dr. Herbert M. Evans, Director, Room 4579, Life Sciences Bldg., University of California, Berkeley.**
(Capacity, 40)
- Tour 2.** **Visit to Radiation Laboratories, University of California, Berkeley, under the direction of Dr. John H. Lawrence. This tour consists of seeing research in progress in the Crocker Laboratory, and viewing the sixty-inch cyclotron; also visiting the Donner Laboratory, there to be shown various phases of research. If circumstances permit, the 184-inch cyclotron will be seen in operation.**
(Capacity, 40)
- Tour 3.** **Demonstration at The Western Regional Laboratory, Department of Agriculture, Albany, under the direction of Dr. Floyd DeEds. Research is being conducted on new uses for food products.**
(Capacity, 40)
- Tour 4.** **Visit to Stanford University. Hoover Library for War, Revolution and Peace, Exhibit on Russian Medicine, under the direction of Dr. George H. Houck, F.A.C.P.**
(Capacity, 40)
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PANEL DISCUSSIONS

The Panel Discussions for the 29th Annual Session are concerned with topics of intimate interest and practical value to all members of the profession. Especially qualified men have been chosen as leaders and members of the panel personnel. These discussions will be held in the Civic Auditorium and in the third floor hall of the Public Health Building from 12:00 M. to 1:15 P.M., Tuesday, Wednesday, Thursday and Friday.

Applications for tickets to Panel Discussions are to be made by members on the regular application forms accompanying the formal program. Tickets will also be available at the Registration Bureau, Main Entrance, Civic Auditorium. Tickets will not be required for admission to Panel Discussions in Polk and Larkin Halls in view of the ample seating capacities of these rooms.

Applicants may submit in writing through the Executive Secretary of the College any questions concerning any phase of the subjects in which they are especially interested. Moderators and panel personnel will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions as time permits.

PANEL DISCUSSIONS

	Polk Hall Civic Auditorium (Admission by badge; no tickets.)	Larkin Hall Civic Auditorium (Admission by badge; no tickets.)	Room 403 Fourth Floor Civic Auditorium (Admission by ticket only.)	Third Floor Hall §Public Health Bldg. (Admission by ticket only.)
Capacity	1,200	800	200	240
Tuesday April 20 12:00 M. to 1:15 P.M.	I Electrocardiography Moderator *George C. Griffith Pasadena *George E. Burch New Orleans *Robert L. King Seattle Maurice Sokolow San Francisco *William D. Stroud Philadelphia William Paul Thompson Los Angeles	II Gastrointestinal Disease Moderator *Philip W. Brown Rochester, Minn. *John H. Fitzgibbon Portland, Ore. Leon Goldman San Francisco *Chester M. Jones Boston *Walter L. Palmer Chicago	III Pulmonary Malignancy Moderator *Sidney J. Shipman San Francisco *J. Burns Amberson New York *H. Corwin Hinshaw. Rochester, Minn. *H. McLeod Riggins New York *John H. Skavlem Cincinnati *Julius L. Wilson New Orleans	IV Virus Diseases Moderator Karl F. Meyer San Francisco William McD. Hammon San Francisco W. Paul Havens, Jr. Philadelphia Albert B. Sabin Cincinnati
Wednesday April 21 12:00 M. to 1:15 P.M.	V Anticoagulant Therapy in Coronary Disease Moderator *Irving S. Wright New York *Nelson W. Barker Rochester, Minn. Herrman L. Blumgart Boston *George R. Meneely Nashville *E. Sterling Nichol Miami John J. Sampson San Francisco	VI Hematology Moderator *Charles A. Doan Columbus, Ohio *Edgar Jones Nashville *Stacy R. Mettier San Francisco *Edwin E. Osgood Portland, Ore. *Cyrus C. Sturgis Ann Arbor *Maxwell M. Wintrobe Salt Lake City	VII Allergy Moderator *Francis M. Rackemann Boston *J. Harvey Black Dallas *Ernest L. MacQuiddy Omaha *Albert H. Rowe San Francisco *John M. Sheldon Ann Arbor *Frank A. Simon Louisville, Ky.	VIII Chemotherapy Moderator *Chester S. Keefer Boston *H. Corwin Hinshaw Rochester, Minn. John Scott Hunt Lexington, Ky. Lowell A. Rantz San Francisco *Wesley W. Spink Minneapolis

PANEL DISCUSSIONS—Continued

	Polk Hall Civic Auditorium (Admission by badge; no tickets.)	Larkin Hall Civic Auditorium (Admission by badge; no tickets.)	Room 403 Fourth Floor Civic Auditorium (Admission by ticket only.)	Third Floor Hall §Public Health Bldg. (Admission by ticket only.)
Capacity	1,200	800	200	240
Thursday April 22 12:00 M. to 1:15 P.M.	<p>IX</p> <p>Hypertension, Medical and Surgical Aspects Moderator *Edgar V. Allen Rochester, Minn.</p> <p>Winchell McK. Craig Rochester, Minn.</p> <p>Kenneth G. Kohlstaedt Indianapolis</p> <p>Howard C. Naffziger San Francisco</p> <p>Myron Prinzmetal Beverly Hills</p> <p>Robert W. Wilkins Boston</p>	<p>X</p> <p>Endocrine Disease Moderator *Hans Lissner San Francisco</p> <p>*Charles W. Dunn Philadelphia</p> <p>*Thomas H. McGavack New York</p> <p>*E. Kost Shelton Los Angeles</p> <p>*Willard O. Thompson Chicago</p> <p>*George W. Thorn Boston</p> <p>*Henry H. Turner Oklahoma City</p>	<p>XI</p> <p>Liver Disease Moderator *Cecil J. Watson Minneapolis</p> <p>*T. L. Althausen San Francisco</p> <p>Gerson R. Biskind San Francisco</p> <p>Roy H. Turner New Orleans</p>	<p>XII</p> <p>Communicable Diseases Moderator Edward B. Shaw San Francisco</p> <p>Henry Brainerd San Francisco</p> <p>Paul M. Hamilton San Marino, Calif.</p> <p>*Conrad Wesselhoeft Boston</p>
Friday April 23 12:00 M. to 1:15 P.M.	<p>XIII</p> <p>Recent Advances in Chest Diseases Moderator *James J. Waring Denver</p> <p>*J. Burns Amberson New York</p> <p>*Arthur L. Bloomfield San Francisco</p> <p>Fred R. Harper Denver</p> <p>Hugh W. Mahon N.C., U.S.A., Denver</p>	<p>XIV</p> <p>Kidney Disease Moderator *Laurence E. Hines. Chicago</p> <p>Frank Hinman San Francisco</p> <p>*Robert K. Maddock San Francisco</p> <p>*Ferdinand R. Schemm Great Falls</p>	<p>XV</p> <p>Psychosomatic Medicine Moderator *Franklin G. Ebaugh Denver</p> <p>*Ward Darley Denver</p> <p>*Edward D. Hoedemaker Seattle</p> <p>*Frederick Lemere Seattle</p> <p>Karl A. Menninger Topeka</p> <p>*Norman Reider San Francisco</p>	<p>XVI</p> <p>Radioactive Isotopes in Medicine Moderator John H. Lawrence Berkeley</p> <p>John W. Gofman Berkeley</p> <p>Charles Heidelberger Berkeley</p> <p>Hardin B. Jones Berkeley</p> <p>Joseph F. Ross Boston</p> <p>Robert S. Stone San Francisco</p>

THE CLINIC SESSIONS

Clinics and demonstrations will be conducted on **Tuesday and Thursday only** from 9:00 A.M. to 11:30 A.M., and Morning Lectures, as previously stated, will be conducted on Wednesday and Friday mornings, thus eliminating competition between these two features of the program. Participating hospitals include:

- A. University of California Hospital
- B. Stanford University Hospitals
- C. Children's Hospital
- D. Franklin Hospital
- E. Laguna Honda Home
- F. Mount Zion Hospital
- G. St. Luke's Hospital
- H. St. Mary's Hospital
- J. San Francisco Hospital
- K. Letterman General Hospital
- L. U. S. Naval Hospital
- M. Veterans Administration Hospital

At several of these hospitals two or more clinics will be running concurrently. Adequate accommodations will be provided for all, but admission will require special tickets which will be issued to members in advance of the Session and to non-members directly at the Registration Bureau in the Civic Auditorium. Application forms for tickets for the clinics will accompany the formal program to all members.

Emphasis will be placed on clinics in the true sense of that word—that is, patients will be shown and discussed rather than having presentations of formal short papers. Scarcely any field of medicine of importance to the clinician has been omitted. In addition to the various aspects of internal medicine, there will be numerous offerings in the allied fields. Opportunities will be afforded for visitors to see patients at close range and observe hospital methods in San Francisco.

The detailed program of clinics is not published in the *ANNALS OF INTERNAL MEDICINE* due to its considerable length, but every detail will be published in the formal program and distributed to all members and to non-members on the official mailing list at the Executive Offices of the College approximately seven weeks in advance of the Session.

ANNALS OF INTERNAL MEDICINE

VOLUME 28

MARCH 1948

NUMBER 3

CONVALESCENCE: A STUDY IN THE PHYSIOLOGICAL RECOVERY OF NITROGEN METABOLISM AND LIVER FUNCTION*

By ROBERT W. KEETON, F.A.C.P., WARREN H. COLE, NATHANIEL CALLOWAY, NATHANIEL GLICKMAN, H. H. MITCHELL, J. DYNIEWICZ
and D. HOWES, *Chicago, Illinois*

CONVALESCENCE embraces the recovery of a multitude of physiological processes in an individual who has suffered from trauma, disease, or an operation. These various physiological processes recover at different rates and the recovery of many is not manifested by any marked objective or subjective signs. There finally comes a time when the patient is conscious of his return to normal and is again ready for work. This transformation from illness to health is often dramatic and is frequently not accompanied by any sign which the physician can detect. The study of convalescence is concerned with the analysis of these disturbances in physiology and an assay of the methods by which recovery can be hastened. The present discussion deals largely with convalescence as illustrated by patients submitted to herniorrhaphy, and is confined to the recovery of nitrogen metabolism and liver function. The general plan of the study and many of the detailed data have been presented elsewhere.¹ Some of the conclusions have appeared also in abstract form.²

THE NITROGEN METABOLISM

The negative nitrogen balance which occurs in fractures and after osteotomy has been attributed to excess catabolism.^{3,4} In the period immediately following the fracture, the intake of food was inadequate and so

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From the Departments of Medicine and Surgery, Chicago, and the Division of Animal Nutrition, Urbana, University of Illinois.

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the metabolic studies were postponed a few days. This depletion of the protein stores would influence the subsequent metabolic periods. Cuthbertson has shown that the oxygen consumption was also increased. This should account for some of the nitrogen loss in Howard's cases, since they were fed relatively low caloric diets in some of the subsequent periods. However, the persistence of the nitrogen losses over longer periods in the case of fractures, and shorter ones in osteotomies, supports Cuthbertson's view that an increased catabolism exists. His work also supports the view that the extra nitrogen is derived from the muscles and not from the local site of injury. The derangement of the nitrogen metabolism in the "alarm reaction" with its increased nitrogen metabolism during the first phase of the general adaptation syndrome (Hans Selye⁵) has been advanced as an explanation for nitrogen losses in injuries and postoperative states. Increased excretion of adrenal corticoids may occur on exposure to low atmospheric pressures with its anoxia,⁶ and might well be responsible for increased gluconeogenesis and nitrogen loss. The view that adrenal activity plays a rôle in nitrogen excretion and its wastage is supported by a number of studies,⁷ which have shown an increased output of urinary corticoids in previously healthy subjects subjected to trauma or infection. The behavior of "debilitated" patients in the presence of infection is in sharp contrast. These patients may exhibit a storage of nitrogen and a low to normal output of urinary cortin. Browne et al.^{7a, b} contend that the feeding of high protein and high caloric diets may mitigate or even overcome the negative nitrogen balance but it does not overcome or prevent the catabolic process. The period during which this anomaly occurs is designated the "catabolic period."

In certain acute infections, especially meningitis and postoperative states, Grossman et al.⁸ have observed similar losses of nitrogen persisting for a considerable time after the acute phase of the disease had subsided. The protein intake was greatly increased, but it did not perceptibly influence the nitrogen balance. Earlier Peters⁹ had emphasized the ability of the poorly nourished individual to conserve protein and attain nitrogen equilibrium in conditions under which the better nourished individual fails. He suggests that there may be a failure in synthesis of proteins and that this varies directly with the severity of the injury and inversely as the state of nutrition. This viewpoint of the failure in synthesis is supported by Albright.^{7c} If further work should confirm the existence of a period of irreparable nitrogen loss, then a method of assaying the immediate severity of an operative procedure or an injury would be available.

On the contrary, the negative nitrogen balances seen in postoperative patients are often due to a disregard for well established nutritional rules which, if applied, would prevent the negative balances.^{7c} Positive nitrogen balances have been maintained after gastric resections and other operations.¹⁰

It has been shown (Strang,¹¹ Keeton¹²) that obese patients subsisting on diets below their caloric requirements, which contain adequate quantities of

protein, use their body fat to replace their caloric deficit without disturbing their metabolism. Thus such patients can store nitrogen, maintain normal metabolic rates¹³ and a minimal nitrogen excretion of 2 to 3 gm. on diets containing calories 30 to 60 per cent below their basal requirements. They show no signs or symptoms of starvation. On the contrary, their sense of well being is increased. If the subject whose stores of fat vary little from normal, as shown by expected weights in actuarial tables, is subjected to a similar diet containing his basal requirements, he will over a period of time develop a negative nitrogen balance, lowered basal metabolic rate, and other changes associated with starvation (Benedict,¹⁴ Lusk¹⁵). If the starvation is pushed to a point at which there has been a 25 per cent weight loss (Keys¹⁶), then the stores of body fat have been reduced 60 per cent and the "tissues" 41 per cent. The fat is unable to protect the body protein and some is retained despite increasing tissue losses. It would be expected that the obese individual and the individual with normal stores of body fat would react as they do normally when convalescing from a surgical procedure. However, this will have to be determined experimentally. It would also be of great practical importance to know the amount of body fat required to protect the nitrogen. These problems are now under study.

Our subjects (figure 1) were normal in body build as shown by their percentage deviation from actuarial standards. A practical clinical rule in-

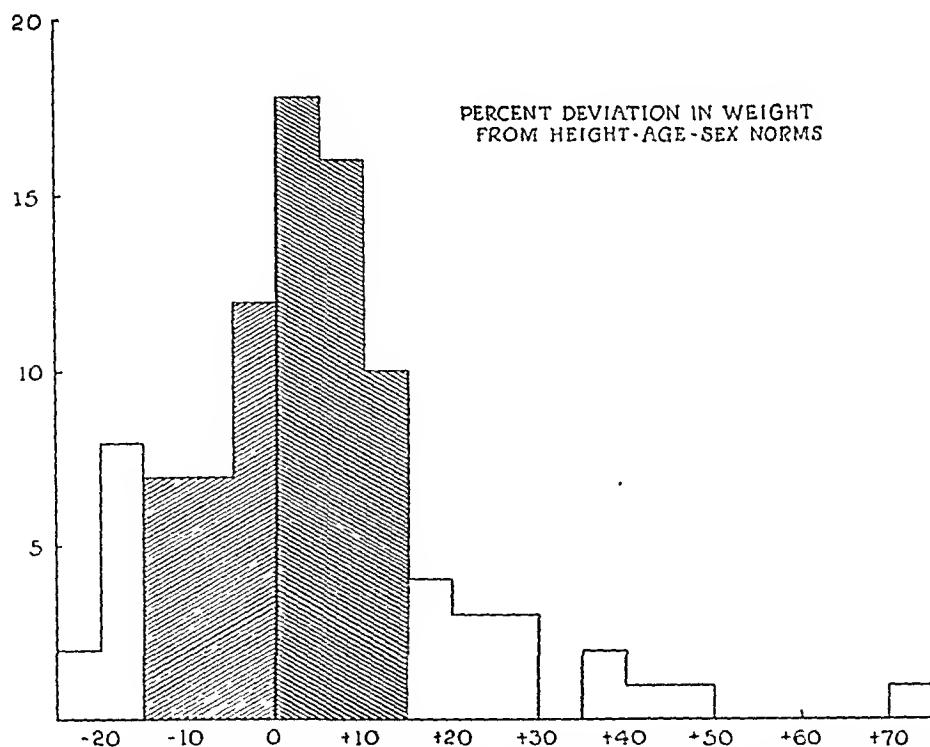


FIG. 1. Distribution of 95 patients submitted to herniorrhaphy, based on the percentage deviation in weight from normal, according to actuarial standards. Ordinate, number of patients; abscissa, per cent deviation.

dicates that obesity begins when the patient is 15 per cent overweight and leanness when he is 15 per cent underweight. By this definition 70 out of 95 patients were normal as to weight. Most of the patients were furnished by selective service boards for correction of their hernias and 85 per cent of these patients were below 47 years of age. They were physically active prior to their entrance to the hospital. Their stores of nitrogen were normal, as shown by the readiness with which they attained nitrogen equilibrium preoperatively. Their body fat would not furnish any significant protection to their body proteins. The herniorrhaphy is to be regarded as a sudden interruption to their normal physiological process. Any observed alterations are to be attributed to the operation and it is to be anticipated that a complete restoration in function would occur. Thus all the conditions for a satisfactory clinical experiment are fulfilled.

In table 1 is found a description of the managements of the groups fed by tube. The feeding through the tube was continued to six hours before

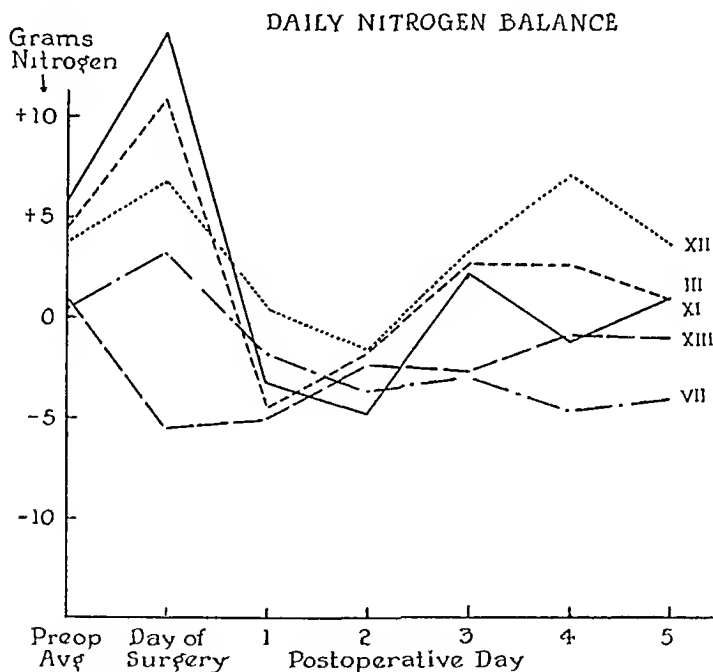


FIG. 2. Average daily nitrogen balance for the groups fed by tube.

the operation and resumed six hours after the operation. This prevented any significant interruption to the nutrition. The courses of the nitrogen balances are depicted in figure 2. In table 2 is found the description of the managements of the groups fed orally. The courses of their nitrogen balances are depicted in figure 3.

The groups (III, XI, XII, VII) which received from 2.75 to 1.21 gm. of protein per kilogram body weight retained from 3 to 14 gm. of nitrogen on the day of operation. By the end of the first or second postoperative days they had lost all of this nitrogen, and on the average, an additional 3.9 gm.

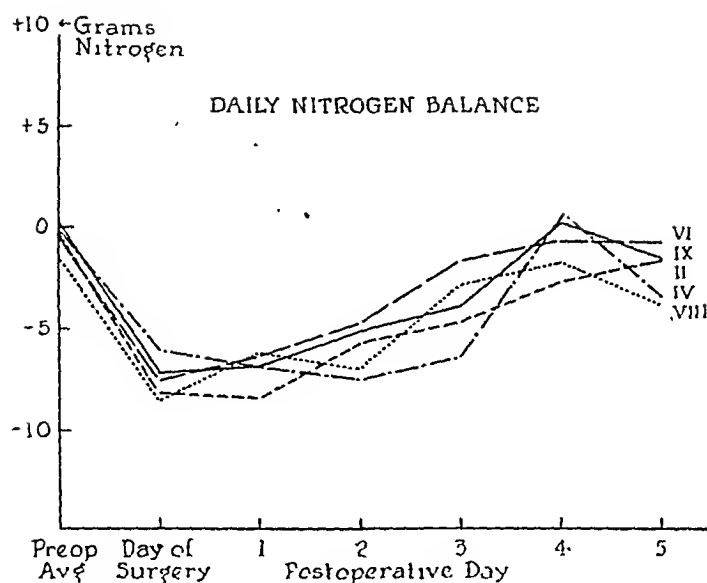


FIG. 3. Average daily nitrogen balance for the groups fed orally.

TABLE I

Description of Management of Groups Fed by Tube* Including Nitrogen Balance on Day of Operation and Five Succeeding Days (see Figure 2)

Group No.	Number of Patients	Daily Calories	Protein		Ambulation	Nitrogen Balance
			Calories Per Cent	gm./kg.		
III†	5	B+100%	20	2.64	+	+10.2
XI	7	B+20%	40	2.70	0	+7.6
XII	5	B+20%	40	2.75	+	+19.4
VII	6	B+20%	15	1.21	0	-13.8
XIII‡	3	B+100%	Level Group VII	1.21	0	-17.5

* Anesthesia: Nitrous oxide induction with ether maintenance in all groups.

† Supplements to diet:

- (a) Preoperatively daily: Orally, choline—1.5 gm., vitamin B complex from yeast—2 tablets 3 times a day, ascorbic acid—200 mg., vitamin A—5000 i.v., vitamin D—500 i.v.
- (b) Day of operation: Orally, choline—1.5 gm., methionine—1 gm. Intravenously, 5 per cent amigen solution in 5 per cent glucose (2000 c.c.). Parenterally, vitamin K—4 mg., liver extract (2 units to 1 c.c.)—5 c.c., adrenal cortical extract—5 c.c., testosterone propionate—10 mg., thiamine chloride—10 mg., riboflavin—10 mg., pyridoxine—5 mg., calcium pantothenate—50 mg., nicotinamide—250 mg., ascorbic acid—200 mg.
- (c) Four succeeding postoperative days: Same supplements as in (b) with omission of methionine and amigen solution.

‡ Feeding schedule group XIII:

Preoperatively, 5th and succeeding postoperative days—protein at same level as group VII, calories, B + 100 per cent.

Day of operation and 1st, 2nd, 3rd, 4th postoperative days—protein levels 0: 0.3: 0.6: 0.9: 1.21 gm. per kg., respectively, calories B + 100 per cent.

The groups (II, IV, VI, VIII, IX) which received no protein and only 50 gm. of glucose by vein lost on the average the day of operation 7.4 gm. of nitrogen.

The group (XIII) which received no protein but basal calories plus 100 per cent, composed of carbohydrate and fat, lost an intermediate amount of nitrogen, 5.5 gm. on the day of operation. The groups receiving protein and maintenance or excessive calories developed a smaller negative balance immediately and returned to a balance more quickly.

However, it would seem that when protein in normal to increased amounts is fed, there is an interference with its retention. If one calculates the average drop from the preoperative levels to the lowest level on either the first or second postoperative days, a value of 7.0 gm. will be obtained.

TABLE II

Description of Management of Groups Fed Orally* Including Nitrogen Balance on Day of Operation and Five Succeeding Days (see Figure 3)

Group No.	Number of Patients	Daily Calories	Protein		Ambulation	Nitrogen Balance
			Calories Per Cent	gm./kg.		
II	10	B+20%	15	1.21	0	-31.4
IV†	6	B+20%	15	1.21	0	-31.3
VI	9	B+20%	15	1.21	+	-21.3
VIII‡	7	B+20%	15	1.21	0	-29.8
IX§	4	B+20%	15	1.21	0	-24.3

* Feeding schedule for all groups:

(a) Preoperatively, 5th and succeeding postoperative days total diet eaten as indicated.

(b) Day of operation, parenteral glucose—50 gm.; protein 0; fat 0.

(c) Four succeeding days, 1/4, 1/2, 3/4, 4/4 of preoperative diet, respectively.

† Anesthesia spinal: In all other groups nitrous oxide induction with ether maintenance.

‡ Supplements same as group III (table 1) plus 4 mg. vitamin K throughout hospital stay.

§ Methionine 2.0 gm. daily during hospital stay.

This is approximately the same as that obtained (7.4 gm.) in groups receiving no protein. This behavior could be attributed to an increase in the catabolism of the protein (Cuthbertson³) or an abeyance in protein synthesis (Peters⁹). The protein has been used for energy purposes but the nitrogen excretion has lagged 24 hours. The period within which this alteration occurs corresponds to the "catabolic period" of Browne and his associates. From a study of figure 2, it would seem that this alteration extended over the day of operation, the first and second postoperative days in those patients (table 1) receiving normal to increased amounts of protein. In the case of those patients receiving no protein on the day of operation and gradually increasing quantities over the next four days (table 2, figure 3; group XIII, figure 2), there was a prompt drop in the nitrogen excretion on the day of operation. However, the gradually increasing amounts of protein given on the succeeding four days were retained. In a herniorrhaphy the disturbance in the nitrogen metabolism has probably passed by

the first and certainly by the second postoperative days. Thereafter the organism functions normally. This time corresponds to the period within which an increased output of cortin was noted by Shipley et al.^{7d} following herniorrhaphy. It would be expected that if the operative trauma were greater, the disturbance in nitrogen metabolism would last longer.

Group XIII which received excessive calories but the same amount of protein as the orally fed groups retained nitrogen more readily and over the six day period lost less (17.5 gm.) than the average of the other groups (27.6 gm.), which received basal calories plus 20 per cent or less. This conservation of nitrogen by the ingestion of extra calories is the expected normal response.

The comparison of groups XI and VII is instructive. Each received basal calories plus 20 per cent. Group XI which received 2.7 gm. of protein per kilo promptly returned to a positive balance of 7.6 gm. for the period while group VII which received 1.2 gm. per kilo showed a negative balance of 13.8 gm. for the period. This would indicate that on a maintenance diet an increase in the proportion of calories from protein is an important factor in reestablishing nitrogen balance and restoring depleted protein stores. Similar conclusions were reached by Werner^{10e} in his studies on patients undergoing subtotal gastrectomies for peptic ulcer.

Group IX, which was fed 2 gm. of methionine daily, showed a negative nitrogen balance of 24.3 gm. as compared with the average balances of groups II, IV, and VIII (30.8 gm.). Group VI is omitted from the comparison because ambulation was a part of the management. This decrease in the negative nitrogen balance is not significant.* No influence of the methionine was noted in decreasing the negative nitrogen balance on the day of operation.

Convalescence as applied to nitrogen metabolism includes not only the attainment of nitrogen equilibrium, but also the repletion of the protein stores. Thus equilibrium may be attained and maintained in the face of a deficit in protein stores (Martin and Robison¹⁷). The slowness with which the nitrogen stores are reconstituted in subjects submitted to low protein diets and to short periods of starvation with or without added carbohydrate has been studied by Kenyon.¹⁸ On refeeding nitrogen equilibrium was attained in six to eight days, but the repletion of the protein stores required a period of three to four weeks' time. Additional calories derived from protein facilitated this repletion, but those derived from carbohydrate were not so effective. In the rehabilitation of normal subjects subjected to relatively severe semi-starvation (Keys et al.¹⁹) the "tissues" were not completely rehabilitated after 32 weeks. Early in the rehabilitation it seemed advantageous to increase the proportion of the calories derived from protein. The prevention of any significant negative nitrogen balance, even though it should last for only a short time, would be highly desirable.

* Student's ^{40, 41} method and tables designated for determining the significance of the mean of a small series of paired differences were used. All data were treated statistically.

Creatine and Creatinine Excretion. The creatine excretions (table 3) of patients in group III who received 2.6 gm. of protein per kilo were significantly greater ($P = 0.020$) than those of patients in groups I, II, and V, who received 1.21 gm. per kilo. This comparison was made on creatine excretions obtained prior to the operation. The difference is attributed to the quantity of meat in the diet.

TABLE III
Creatine Excretion
Effect of Quantity of Protein and Herniorrhaphy

Comparison			Results	
Number	Groups	Periods	Excretion	Probability
1	III* vs. I,† II and V‡	Preoperative	Higher in III	0.020
2	I, II and V vs. I, II and V	Preoperative vs. Day of operation	Decreased	<0.0005
		Preoperative vs. 1st postoperative day	Decreased	0.025
		Preoperative vs. Succeeding post- operative days	Unchanged	—
3	III vs. III	Preoperative vs. Day of operation	Unchanged	—
		Preoperative vs. Succeeding post- operative days	Unchanged	—

* Diet see table 1.

† Regular diet served on surgical ward.

‡ Diet same as group IV, see table 2.

On the day of operation and the four succeeding days the patients in group III received daily injections of 10 mg. of testosterone propionate. Wilkins and Fleischman¹⁹ have shown that testosterone does not produce a creatinuria. Consequently the effects of this procedure can be eliminated from consideration. When the preoperative excretion of creatine in group III was compared with the postoperative excretion, no significant change was noted.

In the members of groups I, II, and V who received much less meat as well as other proteins (day of operation no protein, and first postoperative day 0.3 gm. per kilo) the creatine excretion on these two days was significantly lower ($P < 0.0005$ and $= 0.025$, respectively) than the preoperative

excretion. Since there is considerable variation in the individual excretion of creatine, each patient was compared with himself and the probability computed on this basis. Unless the operation mobilized an endogenous supply of creatine this decrease would be expected.

When the creatinine excretions were studied in a similar manner in group III with high protein intake and in groups IV and V with low protein intake, it was found that herniorrhaphy produced no alterations in the excretions. The wastage of nitrogen, which occurred on the day of herniorrhaphy and two succeeding days in patients receiving by tube diets with normal to increased quantities of protein, did not involve the creatine and creatinine metabolism. The significant decrease of creatine rather than an increase on the day of operation and the succeeding day in patients on diets with low quantities of meat and other proteins and low calories would imply that there was no disturbance in muscle metabolism produced by herniorrhaphy.

INFLUENCE OF AMBULATION ON NITROGEN BALANCE

Taylor et al.²⁰ have shown that in the normal subject at bed rest a negative nitrogen balance accompanied by a reduced blood volume occurred. With reconditioning the nitrogen balance became positive and the blood volume increased. An increased nitrogen output has been noted during the immobilization of healthy subjects in casts.²¹ This output decreased during the recovery period and storage occurred. In a second study²² two of the previous subjects were immobilized in casts, but placed on an oscillating rather than fixed bed. The nitrogen losses were less. The stiffness of the joints and aching of muscles also were less.

There are four groups which may be used for a study of the effect of ambulation on nitrogen balance. Two of these, VI and II, received the same diets (B + 20 per cent) orally, but differed from each other by the addition of ambulation to the management of group VI. These diets contained relatively small amounts of protein during the periods of comparison. Comparison 1, table 4, shows that ambulation very probably decreased the negative nitrogen balance. Groups XII and XI were tube fed with diets high in protein which contained the basal calories plus 20 per cent. Comparison 2 shows no significant difference between the groups. It is probable that the increased protein in the diet masked any effects of ambulation. In comparison 3 the comparable groups with ambulation are contrasted with those receiving no ambulation. However, the type of diets and their methods of administration were entirely different. Consequently the data would be considered as heterogeneous and, therefore, were subjected to an analysis of variance. By this method the data do not indicate a significant difference between ambulated and non-ambulated patients although a considerable probability may be considered to have been established that ambulation does improve the nitrogen balance of a patient convalescing from surgery.

TABLE IV
Effects of Ambulation on Nitrogen Balance Including
Day of Operation and Five Succeeding Days

Comparison	Group Numbers	Number of Patients	Ambulation	Nitrogen Balance	Probability*
1	VI vs. II	6 10	+	-21.3 -31.4	0.036
2	XII vs. XI	5 7	+	+19.4 + 7.6	Insignificant
3	VI and XII vs. II and XI	11 17	+	- 1.9 -23.8	0.058

* The probability favors first group or groups.

Influence of Infection on Nitrogen Metabolism. Surgical procedures in general are accompanied by a rise in temperature. There are many factors which combine to produce these clinically non-significant rises. There is absorption from the devitalized tissues. There may be small areas of patchy atelectasis which reexpand and drain during the first 24 to 36 hours or there may be some disturbance in the fluid and electrolyte balance. The

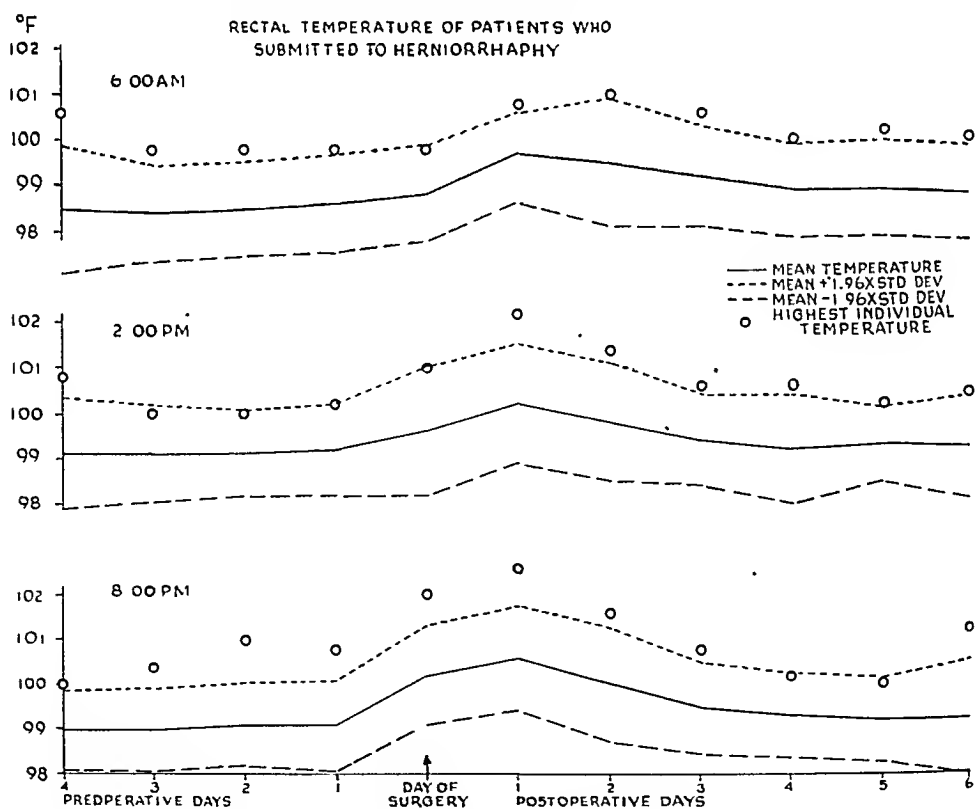


FIG. 4. Daily mean variations in rectal temperatures of 97 patients submitted to herniorrhaphy.

temperature pattern varies with the operation. In order to secure this pattern for herniorrhaphies performed under spinal or general anesthesia (nitrous oxide and ether) an analysis was made of the 97 cases (figure 4) whose postoperative courses showed no complications. On either side of the mean are lines drawn which represent the mean $\pm 1.96 \times$ standard deviation. The chance variations of temperature which are inherent in the operative procedure should fall within the lines. Temperatures which fall outside could be due to an unusual variation in the procedure, or to the introduction of a new factor. It will be noted that the individual variations are few in number and occurred commonly at 8 p.m. both before and after the operation. Perhaps a further word should be added concerning the distinction between the clinically non-significant temperatures described above and those associated with frank infection. In the former the local defenses are operative and the infection is under control. In the latter the infection has escaped from control and the general "alarm reaction" with its accompanying physiological adjustments has been activated.

Any definite elevation of the rectal temperature above this pattern was considered significant and attributed to a complicating infection. Seven such cases occurred in our series. When the nitrogen balance of these seven patients were computed for the day of surgery and the five succeeding days, it was found that they were in marked negative balance as compared with the control members of their groups, who did not suffer from infection. They lost 165.7 extra grams of nitrogen over the average amount lost by their 34 corresponding controls during the same period.

In figure 5 the responses to herniorrhaphy of the control members of group II are shown. These subjects received postoperatively a diet which contained a reduced intake of calories and protein. The calories (basal + 20 per cent) are expressed in terms of the basal requirements, and nitrogen in grams. They received on the day of operation 200 calories as intravenous glucose and no protein, on succeeding days $\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$, and $\frac{1}{4}$ of their preoperative diet. They approximated nitrogen balance on the fifth postoperative day. The 6 a.m. temperature elevations and the efficiency of the liver as measured by the urobilinogen excretion are shown.

In figure 6 is shown the behavior of a patient (J. T.) of group IX who developed a severe wound infection. His temperature was higher and persisted to the tenth postoperative day. The efficiency of his liver as indicated by the urobilinogen excretion was definitely reduced. These findings attest to the severity of the infection. His showing was obviously poorer than the control group. His nitrogen output remained high and the negative nitrogen balance continued as long as the infection remained uncontrolled. He was given protein hydrolysate intravenously on the day of operation and ate all of his prescribed diet thereafter. After the fourth day the diet contained borderline maintenance calories. It is interesting to note that the output of nitrogen paralleled the curve of urobilinogen excretion.

Figure 7 shows the behavior of a patient (L. G.) who developed a postoperative atelectasis. His diet contained much more protein than that of patient J. T. and he received more calories since he was tube fed. His nitrogen balance remained sharply negative until the atelectasis was relieved

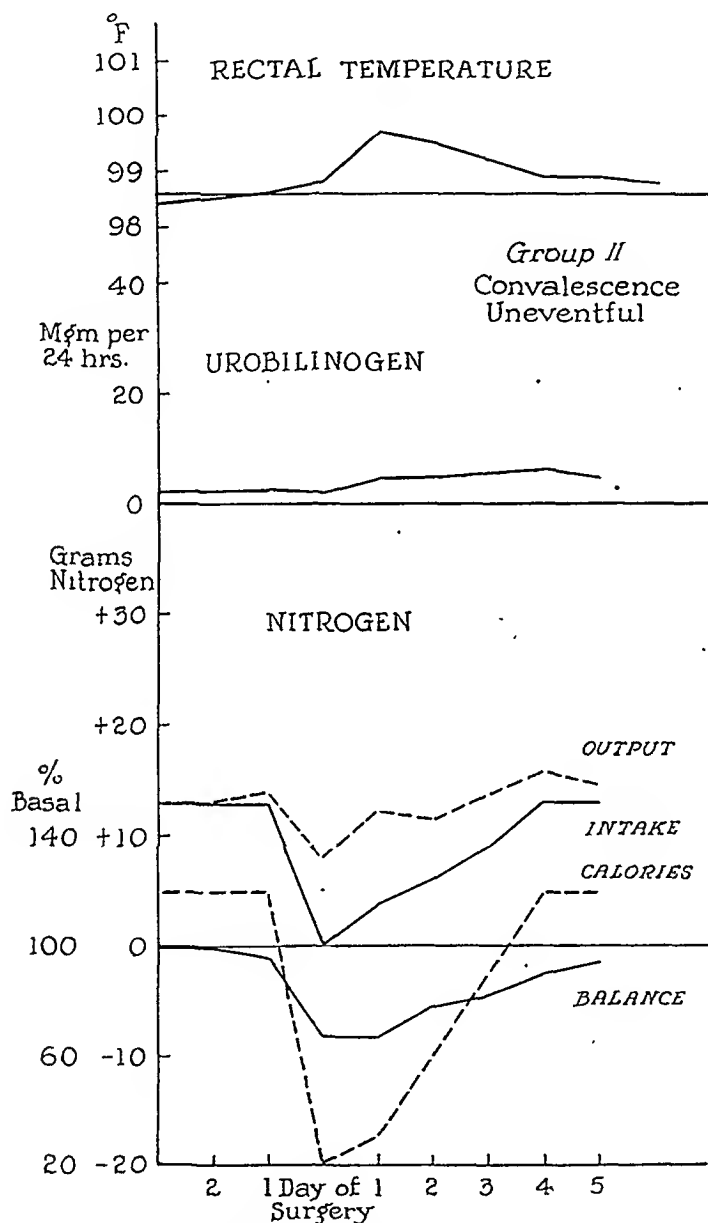


FIG. 5. Average responses of the 10 members of group II who experienced an uneventful convalescence.

and the temperature subsided. The findings in two other cases (L. R. with a pneumonitis and J. K. with a wound infection) corroborate those discussed. In the face of an infection the subjects eat poorly so that it is difficult to determine whether the addition of extra calories would overcome the negative balance or not. It is clear that the subject with an infection

loses more nitrogen than his control, and that an increase in the calories derived from protein does not correct the defect. The nitrogen wastage disappears with the control of the infection.

It would seem likely that the effects of infection and operative procedures on patients are similar and are probably induced by the same mechanisms.

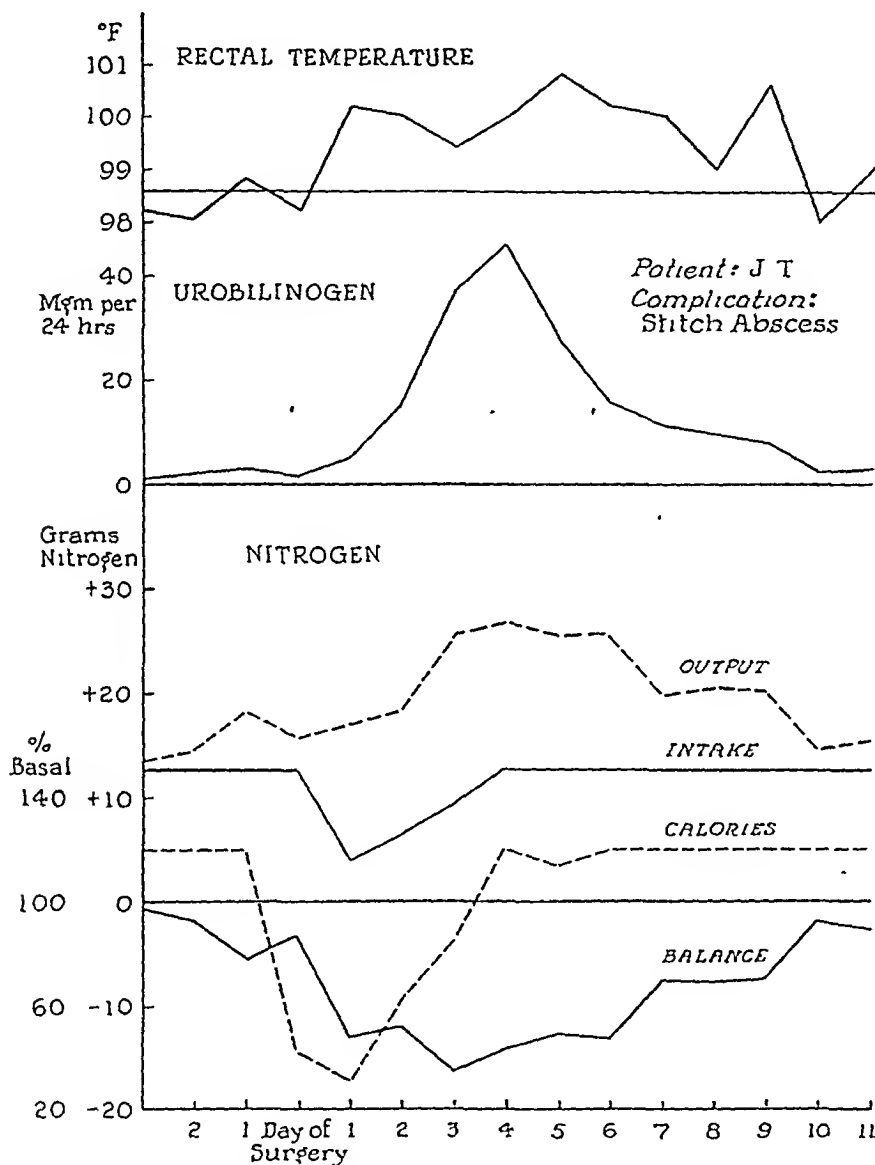


FIG. 6. The responses of a member of group II who developed a stitch abscess.

Further evidence for this view has been furnished by Mann et al.²³ They have reported that the amino acid nitrogen of the blood falls abruptly after injury, operative procedures, and infection. It remains low until recovery is well advanced, even while nitrogen catabolism is greatly increased by the administration of high protein diets. According to Whipple and

associates²⁴ there is a continuous flow of plasma protein out of the circulation into the tissues and vice versa. The condition is described as a "dynamic equilibrium." That this flow of plasma protein results in the rapid exchange of its constituent amino acids has been shown by Fink.²⁵ Lysine

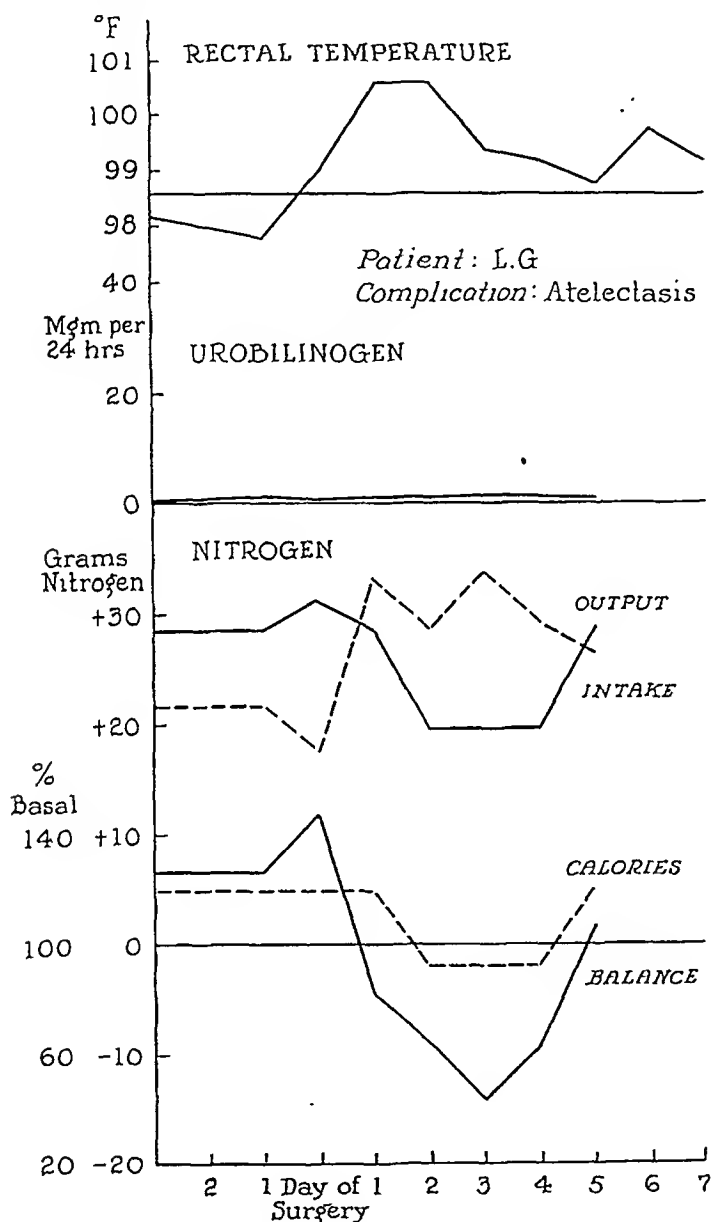


FIG. 7. The responses of a member of group XI who developed an atelectasis.

labeled with heavy nitrogen was incorporated in the serum proteins of a donor dog and its rate of disappearance from the blood of the recipient dog was noted. Within 24 hours, 50 per cent of the labeled protein had been replaced by protein containing normal lysine. With the evidence now at hand that infection also is associated with an increase in the production of cortin, the view of Albright,^{7c} that the "S" hormone diverts amino acids

from protein synthesis to energy requirements, becomes quite acceptable. It furnishes a satisfactory explanation of the abeyance of protein synthesis as suggested by Peters.⁹

Alterations in Liver Function. It was planned in the present study to make, as far as possible, quantitative measurements in the alterations in liver functions, and to determine the protective value of certain therapeutic measures. The information obtained from the various tests will be used to assay the efficiency of the liver, even though there may not be an agreement as to the functions measured.

The literature covering the rôle of the liver in surgery has been recently critically reviewed by Boyce.²⁶ There is no need to present a general discussion of this subject.

It is well understood ^{27, 28} that high concentrations of a volatile anesthetic and any considerable degree of anoxia induced by the anesthetic would produce damage to the liver. The persistence of low blood pressure after a spinal anesthetic would also lead to similar anoxic states.²⁹ Relatively large alterations in blood flow can be induced by physiologic agents (cholinergic and adrenergic substances) in either physiologic or pharmacologic concentrations. Snyder³⁰ has found that with a small dose of a cholinergic agent, the outflow from the hepatic veins can be stopped, the inflow reduced, and the pH shifted during the experiment from 7.45 to 7.39. When such alterations of blood flow are ignored and the inflow is assumed to equal the output, the calculations of glucose and lactic acid added to the liver or subtracted from it varied widely (4 to 2800 per cent for glucose and 5 to 228 per cent for lactic acid). It is easily understood that these factors would produce widespread alterations in the numerous chains of chemical reactions which are a part of the normal physiology of the liver. Recovery periods would be of variable duration.

The operative load includes anesthetic effects, alteration in blood flow, the trauma of the operation, and the effects induced by the absorption of devitalized tissues. There seemed to be no simple objective method available for measuring this load. Since the anesthetics were administered by trained workers and the operations were performed by the regular surgical teams, the time consumed for the herniorrhaphy was used as an index for the operative load.

Urobilinogen Excretion in the Urine. A small amount of urobilinogen normally escapes excretion in the bile and finds its way into the urine. Even though the quantity of urobilinogen is increased in hemolytic conditions, there is no increase in the urine ^{31, 32} unless there is an associated failure of hepatic function. Early parenchymatous changes are revealed by an increase in the urinary urobilinogen and the quantity of urobilinogen in the urine has come to be regarded as a highly sensitive and valued index of liver function. It is therefore most important to determine the range of values for normal subjects.

Watson⁸³ has reported variations between 0 and 4.0 mg. per 24 hours in normal individuals. A series of normals on 84 healthy students, collected by Steigmann and Dyniewicz,⁸⁴ showed average values from 0.27 to 7.67 mg. per 24 hours. These data were made available through one of the authors (Dyniewicz) for further study. An analysis of the average preoperative urinary values in 92 of our patients showed a range of 0.53 to 9.10 mg. per 24 hours. In the series of Steigmann and Dyniewicz four subjects had an average excretion of more than 4 mg. per 24 hours. In our series there were only two patients who had an average excretion more than 4 mg. per 24 hours. In both of these series the same analyst (Dyniewicz) made all the determinations using the same method. The two groups may now be combined into a single group containing 176 normals. An analysis of the average preoperative urinary values for the combined series of patients revealed a range of 0.27 to 9.10 mg. per 24 hours with a mode of 1.24. From the tables giving areas under the normal probability curve it may be shown that 97.5 per cent of the cases will fall on or below 4.4 mg. per 24 hours. ($M + 1.96 \times \text{standard deviation}$.)

Although our patients accepted for herniorrhaphy were in good health, as judged by the history, physical examination and other studies including bromsulfalein clearances, a few showed borderline to high preoperative values for urobilinogen excretion. In this group there were correspondingly high postoperative values. The mechanism for the excretion of urobilinogen seems to have an individually variable block, which may extend somewhat beyond the normal limits. However, any significant increase in the urinary urobilinogen is to be attributed to hepato-cellular damage,⁸⁵ which restrains the escape of urobilinogen into bile and causes it to accumulate in the blood and to appear later in the urine. For this reason it was necessary that each patient act as his own control by the calculation of an individual value for liver efficiency. The daily postoperative efficiency of the liver was expressed as a percentage obtained by dividing the average preoperative excretion by the daily postoperative excretion and multiplying by 100:

$$\frac{\text{Average preoperative excretion in mg.}}{\text{Daily postoperative excretion in mg.}} \times 100$$

Since the urobilinogen excretion approximated normal values in all groups between the fourth and sixth postoperative days an individual score for liver efficiency was calculated for the first five postoperative days. The values for the individual patients were then averaged to give a group score. High values would indicate good hepatic efficiency and low values poor efficiency.

Decrement in Liver Efficiency Measured by Urobilinogen Excretion. By reference to figures 8 and 9 and table 5, the magnitude and the duration of the decrements in liver efficiency can be noted. The excretion of urobilinogen is not strikingly increased on the day of operation but by the third postoperative day the maximal excretion is obtained.

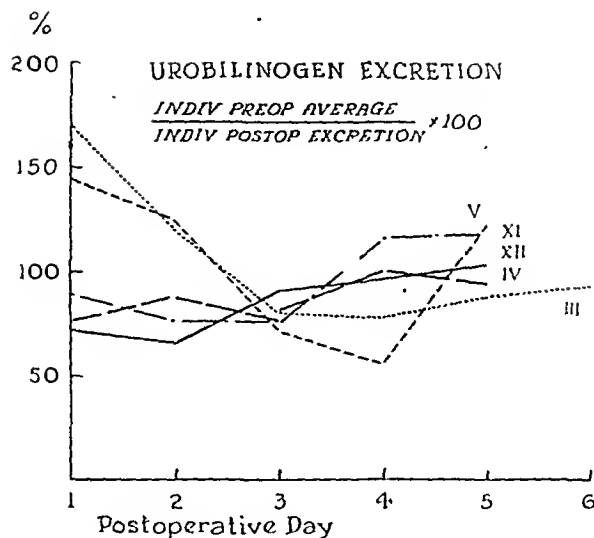


FIG. 8. The efficiency of the liver as measured by urobilinogen excretion in groups making high scores.

The groups (III, IV, V, XI, XII) which had high scores approximated their preoperative excretions on the fourth to fifth postoperative days. The groups (II, VI, VII, VIII, IX, XIII) which had lower scores did not reach their preoperative excretion levels until the sixth or later postoperative days. From the study of the managements of the groups (table 5) it will be noted that two (V and IV) who submitted to spinal anesthesia had high scores. It will be further noted that of the groups submitted to inhalation anesthesia, only three (III, XI, XII) were fed diets high in protein and these had high scores. It is therefore clear that an analysis should be run to determine the significance of these factors.

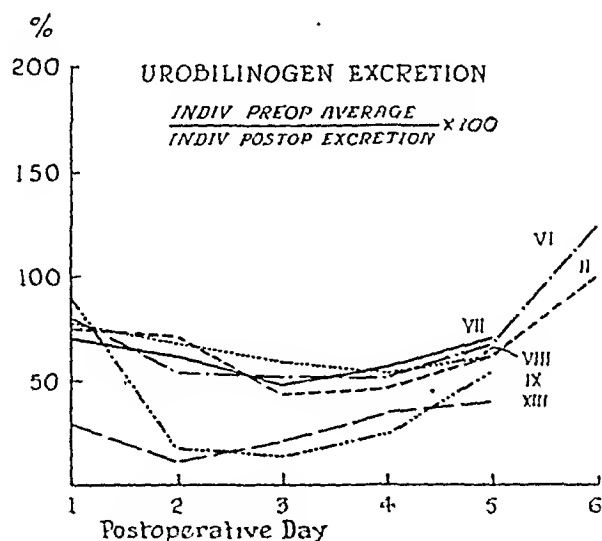


FIG. 9. The efficiency of the liver as measured by urobilinogen excretion in groups with low scores.

Groups II, IV, and V, except for the small amount of ambulation involved in the "Push-Up" test for group V, are strictly comparable and can be used to evaluate the significance of the type of anesthesia. When the 13 patients of groups IV and V were compared with the nine patients of group II they were found to have excreted significantly smaller quantities of urobilinogen ($P = 0.005$). The probability of a chance outcome is so small that it may be ignored, and it is concluded that the spinal anesthetic caused a smaller amount of liver damage as measured by urobilinogen excretion than the inhalation anesthetic. Boyce²⁶ using the Quick³⁸ hippuric

TABLE V
Postoperative Scores of Liver Efficiency Based on Urobilinogen Excretion

Group	Types of Management					Score
	Ambulation	Tube Fed	Calories	Protein	Anesthetic	
III*	+	+	Excessive	High	Inhalation	109
V	Modified	0	Submaint.	Low	Spinal	104
XI	0	+	Maintenance	High	Inhalation	96
XII	+	+	Maintenance	High	Inhalation	86
IV	0	0	Submaint.	Low	Spinal	86
VIII†	0	0	Submaint.	Low	Inhalation	64
VI	+	0	Submaint.	Low	Inhalation	61
VII	0	+	Maintenance	Average	Inhalation	61
II	0	0	Submaint.	Low	Inhalation	60
IX‡	0	0	Submaint.	Low	Inhalation	40
XIII	0	+	Excessive	Low	Inhalation	29

* Supplementation shown in table 1.

† Supplementation same as group III (table 1) plus vitamin K throughout hospital stay.

‡ Methionine 2.0 gm. daily.

acid test compared the effect of ether anesthesia with spinal anesthesia in patients submitted to elective appendectomy and herniorrhaphy. Patients submitted to spinal anesthetic showed a decreased liver function on the first postoperative day, but recovered rapidly thereafter. Those submitted to ether showed definite impairment of function of the liver through the third postoperative day and to a lesser degree through the fourteenth day.

Group XI (eight patients) with a high protein intake can now be compared to group VII (six patients) with an average protein intake. It will be noted that they both received maintenance calories and that their alimentation was maintained by tube feedings. The diet of group VII derived 15 per cent of the calories (73.4 gm.) from protein, 39 per cent (83.6 gm.) from fat, and 46 per cent (225.8 gm.) from carbohydrate. The diet of group XI derived 38.5 per cent of the calories (210.8 gm.) from protein, 22.6 per cent (54.9 gm.) from fat, and 38.9 per cent (212.9 gm.) from carbohydrate. Again there was significantly less urobilinogen excretion by the high protein group ($P = 0.013$). This indicates that a maintenance diet deriving 38.5 per cent of its calories from protein protects the liver signifi-

cantly better than a maintenance diet deriving only 15 per cent of its calories from protein. It may be argued that this beneficial effect cannot be attributed solely to the elevation of the protein (15 per cent to 38.5 per cent) since there was a simultaneous reduction in the fat from 39 per cent to 22.6 per cent. When the actual number of grams of fat (83.6) in the diet of group VII is compared to that usually taken by subjects under the dictates of the appetite, it would be moderate to low in value. It is in no sense of the word high. A value of 54.9 gm. (group XI) would be regarded as definitely low. Wilson, Pollock and Harris⁴³ have found no difference in the rate of recovery of patients suffering from hepatitis on diets containing respectively 202 gm. and 68 gm. of fat per day. Hoagland^{42, 44} also has indicated that patients recover more readily from infectious hepatitis on diets containing 150 gm. of fat and 150 gm. of protein than on diets containing 50 gm. of fat and 150 gm. of protein. It would seem justifiable to attribute the protective value of the diet fed to group XI to the increase in protein rather than a reduction in fat. Ambulation did not alter significantly the urobilinogen excretion. In making comparisons, groups which received ambulation, and those which received no ambulation may be treated as strictly comparable. Group III may now be compared with group XIII and again the patients receiving the high protein diet (III) excreted significantly less urobilinogen ($P = 0.006$).

In a comparison of groups XI and XII with groups VI, VII, VIII and IX, the results again favor the groups with a high protein diet ($P < 0.005$). The former groups received maintenance calories and high protein; the latter received either maintenance or submaintenance calories and low protein.

Finally, when all groups (III, XI and XII) receiving high protein diets are compared with those receiving low protein diets (VI, VII, VIII and IX), disregarding the variation in the number of calories (submaintenance to maintenance) derived from carbohydrate and fat, the urobilinogen excretion is significantly lower in the high protein groups ($P < 0.005$).

When group VII (six patients) was compared with group II (nine patients) it was found that the continuous alimentation of a diet containing basal calories plus 20 per cent with 15 per cent of calories from protein was no more effective in protecting the liver than the oral ingestion of a somewhat smaller quantity of the same diet. In group XIII the calories in the diet were increased to basal plus 100 per cent using extra carbohydrate and fat, but the protein was maintained at the same level as group II. In group II the subjects ate postoperatively on successive days $\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$ and $\frac{1}{4}$ of their diet consisting of basal calories plus 20 per cent with 15 per cent calories from protein. When these two groups were compared it was found that the urobilinogen excretion was significantly less in group II ($P = 0.011$). The ingestion of extra calories derived from fat and carbohydrate seemed to lessen the efficiency of the liver. It is likely that the offending agent was the extra fat.

Infections and Urobilinogen Excretion. The excretion of urobilinogen of patient J. T., who developed a severe infection at the site of the repair of his hernia, is shown in figure 6. This should be compared with the urobilinogen excretion in the controls submitted to the same management, figure 5. It will be noted that the curve of excretion paralleled that of the nitrogen. The increase began at the close of the first postoperative day and returned to a normal value on the tenth postoperative day, at a time when the infection was under control. In figure 7 is found the urobilinogen excretion of L. G., who developed an atelectasis. The excretion remained within normal limits, and could be due to an absence of infection back of the obstruction. However, the nitrogen excretion rose and the nitrogen balance became negative. In the five other subjects with infection there was an increased urobilinogen excretion which returned to normal with the control of the infection.

One is impressed with the similarity in the behavior of the nitrogen and urobilinogen excretions in the presence of infection. Whether the wastage of nitrogen is to be attributed to an increased catabolism of amino acids or a failure in the synthesis of proteins, the similarity of the effects of infection on the excretion of these two constituents would indicate that the site of action is more probably on the cells of the liver than on the muscles.

Bromsulfalein Excretion. Description of test and method of scoring. Five milligrams per kilo body weight of the dye was injected intravenously. Samples of the blood were drawn at 30 and 40 minute intervals. The sum of the percentages of the dye retained at these intervals gave a numerical value for the test. All the preoperative values of dye retained by each member of a group were averaged to obtain a group value. The same procedure was followed postoperatively. Tests were run preoperatively on two days, and postoperatively on the first, third, and fifth days. A group score for the efficiency of the liver was obtained by the expression:

$$\frac{\text{Preoperative retention in per cent of dye}}{\text{Postoperative retention in per cent of dye}} \times 100.$$

This group treatment of the data was necessitated by the not infrequent preoperative zero retention of dye, despite the sampling of the blood at the 30 minute interval.

Examination of figure 10 reveals that there is an immediate drop in the score and that there is progressive recovery with a return to normal on the fifth or later postoperative day. Alterations in the diet, the addition of dietary supplements, and ambulation do not influence the function of the liver as measured by this test. Infection, on the other hand, definitely reduced the scores (table 6).

Prothrombin Percentages. Using Quick's method³⁷ studies in prothrombin percentages were made preoperatively and on the third and fifth postoperative days in five groups. In some groups relatively unimportant decreases were noted on the third postoperative day. Even in the group

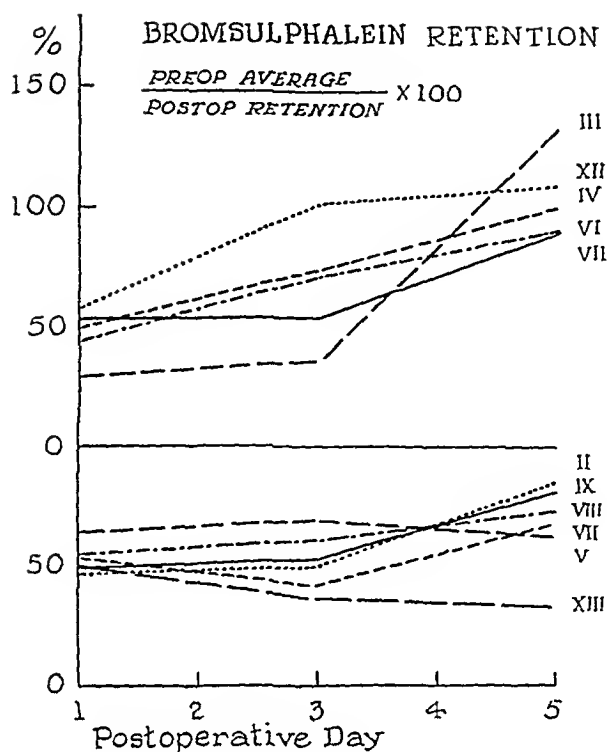


FIG. 10. The efficiency of the liver as measured by bromsulfalein retention for all groups.

TABLE VI
Bromsulfalein Retention of Patients with Complications Using Determinations on the First,
Third and Fifth Postoperative Days $\frac{\text{Preoperative}}{\text{Postoperative}} \times 100$ Expressed in Terms
of Per Cent of Preoperative Efficiency

Patient	Control* Complication	Score in Per Cent of Preoperative Efficiency
T	Stitch Abscess	36
	Control Group IX	61
K	Wound Infection	41†
	Control Group III	66
M	Pneumonia	31
	Control Group XI	54
L	Pneumonitis Atelectasis	23
	Control Group II	60
S	Cystitis	46
	Control Group IX	61
B	Coronary Thrombosis	38
	Control Group VIII	63

* Other members of same diet group who suffered no complications.

† Preoperative retention 0; a value of 1.0 was assumed for sake of computation.

(II) which subsisted preoperatively on maintenance to submaintenance diets and postoperatively on $\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$, and $\frac{4}{4}$ of this diet on successive days, there was no serious impairment of the prothrombin percentage by herniorrhaphy. However, group V which received spinal anesthesia showed a slight increase rather than a slight decrease as shown in group II. The difference between the two groups was significant ($P = 0.016$) and confirms the findings of Borgstrom³⁸ that patients who submitted to spinal anesthesia maintain their prothrombin indices more consistently than those who submitted to general anesthesia. It is possible that heavier operative loads might show significant impairments.

Alterations in Serum Total Cholesterol and Cholesterol Esters. In parenchymatous lesions of the liver there is some reduction in esterification of the cholesterol with a decrease in esters.^{8, 39} Studies were made of the post-

TABLE VII

Effect of Operative Load in Producing Alterations in the Serum of Total Cholesterol, Cholesterol Esters, and Per Cent Cholesterol Esters

Group		Management	Preoperative Average mg./100 c.c.		Probability† Postoperative Days			
No.	No. of Subjects				3	5	7	11
Cholecystectomy								
XV	5	B+40% 15% protein ether+nitrous oxide	Total cholesterol Cholesterol esters Percentage esters	254 199 78.5	0.011 0.008 0.015	— — —	* 0.038 *	* * *
XVI	3	B+40% 15% protein spinal anesthesia	Total cholesterol Esters Percentage esters	265 212 79.3	0.004 0.009 .	* * *	* * *	* * *
Herniorrhaphy								
XIV	4	B+40% 15% protein ether+ nitrous oxide	Total cholesterol Esters Percentage esters	246 216 87.8	0.005 0.005 *	* * *	— — —	— — —

* Changes not significant.

† Refers to decrease postoperatively.

operative alterations in cholesterol and cholesterol esters in group XIV (herniorrhaphy), group XV (cholecystectomy, nitrous oxide and ether anesthesia), group XVI (cholecystectomy, spinal anesthesia). The managements of these groups otherwise were similar. It will be noted (table 7) that significant reductions were found on the third day in all three groups but a reduction of only probable significance was found on the seventh day in the esters of group XV. As measured by alteration in this function neither herniorrhaphy nor cholecystectomy appears to be a heavy load.

Alterations in Serum Total Proteins, Albumin and Globulin. Alterations in the serum proteins were studied in group XIV, group XV, and group XVI (table 8). It will be noted that in groups XV and XIV, which were submitted to nitrous oxide and ether anesthesia but different operations, there were significant changes in serum total proteins and albumin on the third postoperative day. Following the herniorrhaphy the changes had disappeared by the fifth day but they persisted after the cholecystectomy through the eleventh day. Following cholecystectomy under spinal anesthesia the changes in the albumin were suggestive but at no time definitely

TABLE VIII
Effect of Operative Load on Serum Total Proteins, Albumin and Globulin

Group No.	No. of Subjects	Management	Preoperative Average gm./100 c.c.	Probability† Postoperative Days			
				3	5	7	11
Cholecystectomy							
XV	5	B+40% 15% protein ether + nitrous oxide	Total proteins 6.47 albumin 3.87 globulin 2.60	0.022 0.009 *	0.022 — *	* 0.004 *	0.039 0.011 *
XVI	3	B+40% 15% protein spinal anesthesia	Total proteins 6.59 albumin 4.14 globulin 2.45	* 0.045 *	* 0.045 *	* 0.015 *	* 0.041 *
Herniorrhaphy							
XIV	4	B+40% 15% protein ether + nitrous oxide	Total proteins 6.75 albumin 4.26 globulin 2.49	0.012 0.014 *	* * *	— — —	— — —

* Changes not significant.

† Refers to decrease postoperatively.

P < 0.030, significant.

P > 0.030 < 0.045 of suggestive significance.

significant. This would indicate that the proteinogenic function of the liver is definitely impaired after cholecystectomy under nitrous oxide and ether anesthesia, but not after herniorrhaphy.

Exton-Rose Glucose Tolerance Test. The alterations in this test in patients submitted to herniorrhaphy were found to be negligible and so complete studies of all the groups were not made.

Studies were made in groups XV and XVI submitted to cholecystectomy. An analysis of the data revealed no significant differences in the behavior of these two groups when compared with each other either pre- or post-operatively.

After operation the fasting blood sugars (table 9) are significantly elevated. Since the fasting blood sugar levels were significantly altered

postoperatively the direct comparison of the pre- and postoperative 30, 60 and 120 minute values were not considered valid. Therefore the fasting values were subtracted from the subsequent values and an analysis made of the increments over the fasting levels. The probabilities on the comparisons thus made are shown in table 9. This would indicate that the ability of the liver to control blood sugar levels is altered for 10 days following cholecystectomy.

Other Liver Function Tests. Other tests of liver function were tried out in our preliminary studies and discarded as unsuitable for our purposes.

TABLE IX
Alterations in Liver Function Following Cholecystectomy Measured by
Exton-Rose Glucose Tolerance Test

Time of Test	Groups	Comparison: Preoperative Value vs. Postoperative Value	
		Probability* on fourth day	Probability on tenth day
0 fasting	XV and XVI	0.010	†
30 minutes		†	†
60 minutes		0.039	<0.001
120 minutes		0.003	<0.001

* Refers to increase postoperatively.

† Change is not significant.

Simultaneous measurements were being made of physical performance and some of the patients were being submitted to ambulation. An excessive number of venipunctures interfered with these tests. For this reason intravenous glucose and galactose tolerance tests, and hippuric acid tests were discarded. The oral hippuric acid which is a valuable test interfered with our feeding schedules. The cephalin flocculation test was discarded because of variable results.

Effect of Excess Intake of Supplements and Vitamins on Efficiency of Liver. Early in our studies it seemed advisable to add to the management of one group all the factors that might conceivably facilitate convalescence. This group (III) made the highest score on the basis of all tests applied. Included in the management were the supplements described in a footnote to table 2. Again it should be emphasized that there was no reason to believe that these normal healthy subjects were deficient in vitamins. In order to analyze more specifically the effects of these supplements, they were added to the control management used for group II. Groups II, VIII, and IX are strictly comparable except as to vitamins and supplements. Group VII was also available for comparison. In this group the same diet was fed but the postoperative interruption to the alimentation was prevented by tube feeding. From table 10 it will be noted that the efficiency of the liver was the same in all of those groups as measured by urobilinogen excretion and brom-

TABLE X

Effect of Excess Intake of Vitamins and Supplements on Liver Function

Group No.	Management	Urobilinogen Score	Bromsulfalein Score	$\frac{\text{Prothrombin Score Postoperative percentage}}{\text{Preoperative percentage Postoperative Day}} \times 100$	
				Third	Fifth
II	B+20% 15% protein	60	60	89	91
VII	B+20% 15% protein tube fed	61	66	85	100
VIII*	B+20% 15% protein supplementation	64	63	115	116
IX†	B+20% 15% protein Methionine	40	61	—	—

* Supplements described in table 1, group III, with addition of vitamin K 4 mg. daily during hospital stay.

† Methionine 2 gm. daily during hospital stay.

TABLE XI

Effect of Operative Load

Day of Operation and Five Succeeding Days, Measured by

Liver Efficiency (a) $\frac{\text{Preoperative Urobilinogen Excretion}}{\text{Postoperative Urobilinogen Excretion}} \times 100$

(b) $\frac{\text{Preoperative Bromsulfalein Retention}}{\text{Postoperative Bromsulfalein Retention}} \times 100$

Nitrogen Balance in Grams

Group		Management	Urobilinogen Score	Bromsulfalein Score	Nitrogen Balance gm. 6 days
No.	No. of Patients				
Cholecystectomy					
XV	5	B+40% 15% protein Nitrous oxide+ether	48	40	-31.1
XVI	3	B+40% 15% protein Spinal anesthesia	32	14	-29.0
Herniorrhaphy					
XIV	4	B+40% 15% protein Nitrous oxide+ether	60	47	-16.2

sulfalein clearances. In group VIII 4 mg. of vitamin K daily during the period of hospitalization was added to the supplements (group III, table 2). The questionably higher percentage of prothrombin is doubtless to be attributed to this specific factor.

Comparison of Operative Loads in Herniorrhaphy and Cholecystectomy. From tables 7, 8, 11, a comparison can be made of the operative loads of cholecystectomy and herniorrhaphy as revealed by objective tests.

There was a greater impairment in liver function tests in cholecystectomy. The urobilinogen excretion was greater, bromsulfalein clearance was somewhat more reduced, the serum proteins were altered longer, and the glucose tolerance test was altered through the tenth postoperative day.

In herniorrhaphy there was no significant alteration in the glucose tolerance test. The changes in serum proteins disappeared after the third postoperative day. The negative nitrogen balance for the day of operation and five succeeding days was greater after cholecystectomy. The clinically non-significant elevations in temperature associated with cholecystectomy were greater and persisted for a longer time. Boyce²⁶ compared 10 patients submitted to elective appendectomies and herniorrhaphies with 34 patients submitted to cholecystectomy using the hippuric acid test. There was surprisingly little difference in the behavior of the two groups after the third postoperative day. The cholecystectomy group showed a 65 per cent excretion of hippuric acid on the first postoperative day as compared with an 88 per cent excretion by the other group.

SUMMARY

1. Data on convalescence from herniorrhaphy and cholecystectomy as it concerns nitrogen metabolism and the functions of the liver have been presented. Unless otherwise stated the conclusions apply specifically to herniorrhaphy.

2. The nitrogen excretion on the day of operation and five succeeding days was the same under an inhalation anesthetic (nitrous oxide and ether) as under a spinal anesthetic.

3. Patients who received orally postoperatively a diet containing maintenance calories and protein showed a maximal negative nitrogen balance on the day of operation. With an increase in the diet there was a progressive return toward a positive balance by the fifth day or shortly thereafter.

4. Patients who received by tube a diet containing basal calories plus 20 per cent to basal plus 100 per cent and protein 1.2 to 2.7 gm. per kilo of body weight, retained nitrogen on the day of operation but developed a negative balance on the first or second postoperative days. The rate of return to a positive nitrogen balance was facilitated by an increase in calories derived from protein.

5. In patients who received a diet containing basal calories plus 100 per cent and low protein (0.0:0.3:0.6:0.9 and 1.2 gm. per kilo on succeeding

days), the negative balance was less than in the groups receiving a smaller calorie intake and the same amount of protein.

6. This wastage of nitrogen which occurred on the day of operation and the first and second postoperative days was seen in subjects to whom generous supplies of protein were given.

7. After this period of wastage has passed the patient behaves normally with respect to the conservation of nitrogen. This period may be of such short duration as to be obscured by its inclusion in a longer collection period. However the magnitude and the duration of the wastage should be a valuable index of operative trauma.

8. A positive nitrogen balance for the period covered by the day of surgery and five succeeding days was maintained by the following regimes:

- (a) Diet containing excessive calories ($B + 100$ per cent) and excessive protein (2.6 gm. per kg.), administered by tube.
- (b) Diet containing maintenance calories ($B + 20$ per cent) with 40 per cent calories from protein (2.7 gm. per kg.), administered by tube.

This positive balance observed in (b) was augmented by the addition of ambulation.

9. A negative nitrogen balance for the period covered by the day of surgery and five succeeding days occurred under the following regimes:

- (a) Diets containing maintenance calories (basal $+ 20$ per cent) and an average amount of protein (1.2 gm. per kg.), administered by tube.
- (b) Diets containing excessive calories ($B + 100$ per cent) and protein at low levels (day of operation 0.0 gm., succeeding days 0.3:0.6:0.9 and 1.2 gm. per kg.), administered by tube.

Ambulation reduces but does not abolish the negative balance of patients receiving diets containing submaintenance calories and low protein.

10. Wastage of nitrogen with negative balances followed promptly the onset of infection. It is not corrected by diets containing submaintenance calories and increased quantities of protein. It is corrected by the control of the infection.

11. The efficiency of the liver was measured by the quantity of urinary urobilinogen. This proved to be a delicate index of parenchymatous liver damage. The maximal excretion occurred on the third postoperative day and the excretion returned to normal by the sixth day.

It was reduced by diets containing (a) excessive number of calories and 2.6 gm. of protein per kg., (b) maintenance calories and 2.7 gm. of protein per kg.

It was not influenced by continuous alimentation (tube) of diet containing maintenance calories and 1.2 gm. protein per kg., as compared to the discontinuous oral ingestion of reduced amounts of the same diet.

The excretion was increased in a group of patients who received by tube a diet containing excessive calories (B + 100 per cent) and low protein (0.0:0.3:0.6:0.9: 1.2 gm. per kg. on succeeding days), as compared to a group who received by discontinuous oral ingestion a diet containing sub-maintenance calories and the same quantities of protein. The increased excretion of urobilinogen may be attributed to a disproportion between the increased fat (130 gm.) and the low protein. The protein present may not furnish adequate number of labile methyl groups.

The excretion of urobilinogen was not influenced by ambulation.

The excretion was increased with the onset of an infection and was reduced with the control of the infection.

12. The maximal retention of bromsulfalein following herniorrhaphy occurred on the day of operation. The clearance was normal by the sixth or later postoperative days. Alterations in diet, the addition of dietary supplements, and ambulation did not influence the function of the liver as measured by the test. The effects of infection on this function of the liver were definite also.

13. Excess quantities of vitamins and other supplements, including 2 gm. of methionine daily, exerted no protective influence on liver function as measured by urobilinogen excretion and bromsulfalein clearances.

14. Herniorrhaphy produced no marked decreases in prothrombin percentages. There were significant decreases in total serum proteins and albumin on the third postoperative day which were absent on the fifth day. There were significant reductions in total cholesterol and cholesterol esters on the third postoperative day only. There were no significant changes in fasting blood sugars or in the Exton-Rose glucose tolerance test.

15. After cholecystectomy there were significant changes in the fasting blood sugars on the fourth postoperative day and in the Exton-Rose glucose tolerance test as late as the tenth postoperative day. The total cholesterol and cholesterol esters were reduced on the third postoperative day, but not thereafter. The total serum proteins were significantly reduced on the fifth postoperative day and the serum albumin as late as the eleventh postoperative day.

16. Judged by purely objective tests the operative load of cholecystectomy was definitely heavier than that of herniorrhaphy. In addition to differences enumerated under 14 and 15 the urobilinogen excretion, the bromsulfalein retention, and the negative nitrogen balance for the period, including the day of surgery and the five succeeding days, were all greater after cholecystectomy. The clinically non-significant rises in temperature were somewhat greater and persisted for a longer time.

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THE HUMAN FACTORS IN HIGH PERFORMANCE AIRCRAFT *

By B. GROESBECK, JR., Rear Admiral (MC), USN, *Washington, D. C.*

ABOUT three years ago I had the honor of addressing the New Orleans regional meeting of this College on the subject of Aviation Medicine and with what now appears to be rather unbecoming smugness, I at least intimated that the physiological problems incidental to military flying were well on their way toward final solution. Events, however, have proved that such is not the case. The aircraft designers have come forth with new planes whose performances in the air present new questions in environmental physiology to which as yet we do not have the answers. These answers, however, must be provided since in high performance aircraft human factors become more and more important. As a matter of fact, aircraft designers are now giving considerable thought to the man who is to fly the plane because after all, it is the human limitation which will limit piloted aircraft performance and the closer the speed of the airplane approaches the speed of sound, the more important become these limitations of man.

To fully discuss the human factors in high performance aircraft would take more time than is allowed here and it will be possible to mention only a few of the many problems which face us, in particular those related to the design and performance of military aircraft. As an index of the multiplicity of questions which must be answered, it is of interest that the major portion of the medical research program on which the Navy has embarked deals with problems which are directly, or indirectly, related to Aviation Medicine and this research is being undertaken not only in the laboratories of the Navy, but also in the Army and in many universities throughout the country.

The first of these problems we will discuss is that of oxygen supply. At the present time the armed forces are using diluter-demand oxygen systems which automatically increase the amount of oxygen breathed as the altitude increases, but since the amount of oxygen available to a pilot depends on the partial pressure of that gas in the alveoli of the lung, there is naturally a limit to the usefulness of this particular system. Actually, at the altitude of approximately thirty-four thousand feet, at which altitude the present automatic valve supplies 100 per cent oxygen to the nose and mouth of the user, there is provided an alveolar oxygen pressure of only about 100 millimeters of mercury, because of the presence in the alveoli of water vapor and carbon dioxide. This is approximately the condition existing when breathing air at sea level. It is obvious that with this oxygen system, further ascent and further result-

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The opinions contained in this paper are those of the author. They are not to be construed as necessarily reflecting the views or the endorsement of the Navy Department.

ing reduction in ambient pressure will cause a decrease in the partial pressure of oxygen and in the subsequent development of anoxia.

From the use of this diluter-demand system, it was a logical step to proceed with the development of pressurized systems which would supply the flier with oxygen under a positive pressure greater than that of the ambient air and thereby increasing the alveolar oxygen pressure. This development has produced satisfactory results in the design of pressurized valves and masks and has definitely increased the human ceiling by preventing the development of anoxia. However, this increase has not been proportionate to the increase in potential ceilings of new aircraft and we are still searching for further improvements which will result in preventing anoxia at high altitudes.

Another development is the introduction of pressurized cockpits. It is entirely possible to build a cockpit which could be maintained at sea level pressure when flown to any altitude. However, the loss in performance of such a craft, because of the strength and weight of the structures involved, would make its construction impracticable. The principle of the cockpit pressurization, however, has been adapted to actual use by pressurizing the cockpit to a lesser degree. Under such conditions, the pilot can reach a relatively high altitude without the use of oxygen and when oxygen is used in addition to pressurization, the pilot can reach much higher altitudes than possible with the conventional oxygen systems used in an open cockpit. Another factor which governs the degree to which cockpits can be pressurized is the possibility of explosive decompression which occurs when the cockpit is punctured, a hazard to which the military pilot would naturally be exposed. It is, therefore, necessary that a reasonable differential be maintained between the cockpit pressure and the ambient pressure in order to prevent damage to the viscera and possible fatal injury should the cockpit seal be ruptured.

There recently took place at the U. S. Naval Air Station, Pensacola, Florida, an experiment which was designated "Operation Everest." This project was designed to determine the effect of acclimatization on the development of altitude anoxia. In carrying out the project, four volunteers spent one month in a low pressure chamber during which time they were subjected to a gradual decrease of air pressure and eventually were carried to a simulated altitude of about 29,000 feet. At that altitude the subjects existed quite comfortably and performed work without the use of additional oxygen in a manner comparable to that of a non-acclimatized man at 23,000 feet. During the course of the experiment, numerous tests were performed on each of the subjects which required frequent rapid ascents on the part of the attending personnel in order to secure the respiratory, blood, and other specimens for laboratory study. Although these attendants were not exposed to low pressures for long intervals and although none were required to reach 30,000 feet, it is interesting that about one-third of these young men eventually developed symptoms of aero-embolism.

On the basis of our knowledge of aero-embolism, one would not expect those symptoms to occur at such relatively moderate altitudes and the question arises, therefore, as to the causation of unexpected aero-embolism in these cases. If the rate at which the attendants were elevated to the simulated altitude is the factor of importance, then preventive measures must be developed because modern airplanes can climb faster than these persons were elevated in the chamber. If, on the other hand, the responsibility for the development of acquired susceptibility to aero-embolism rests on rapidly repeated exposures to low pressures, then it is obvious that military missions for a combat pilot would have to be limited in number or a particular preventive device developed. At the present time, further investigation is being undertaken in an attempt to provide the answer to this interesting problem.

Another problem which is of great interest to the pilot is the question of escape from damaged high speed aircraft. The classical methods of parachute escape cannot be used in the more modern planes because of their construction and because of their performance characteristics. The danger of acute anoxia when abandoning a plane at high altitude may be largely counteracted by the use of the so-called bail out bottle which will provide sufficient oxygen for the parachute descent, but there are also to be considered the questions of wind blast and deceleration as well as the problem of clearing the tail surfaces when leaving the plane.

The answer to the last problem can be found in forcible ejection of the pilot from the airplane, and at the present time ejection seats have been developed which will throw the pilot out of the cockpit with sufficient force and speed to prevent physical injury from contact with the plane's tail assembly. During these ejections, which are accomplished by a powder blast, the pilot is subjected to acceleration up to about 16 "G." Since this is a considerable force, care must be exercised to properly position the pilot prior to ejection in order to prevent injury to the vertebrae.

In all military planes of present design, the tail surfaces, including the horizontal and vertical stabilizers, are placed above the lower surface of the fuselage and it would appear that ejection of the pilot downward instead of upward would be a more desirable method of escape. Obviously, this procedure would not subject the individual to as great a degree of acceleration as does the upward ejection since there would be no danger of contact with the tail surfaces and since the escape would be facilitated by the effect of gravity. Unfortunately, however, whatever acceleration is applied to eject the pilot downward would occur in a foot-to-head direction. We have some idea of the human tolerance to the force of acceleration when applied in the direction of head-to-foot or when applied in a direction transverse to the body, but we are not so well informed regarding tolerance when the acceleration is applied in the foot-to-head direction. We do know, however, that this position is the one in which humans are least able to withstand acceleration

and, until the investigation is completed, we are reluctant to adopt the downward means of ejection.

In addition to the danger of injury from contact with the tail surfaces, ejection from fast aircraft may take place at such speeds as to subject the pilot to the effects of excessive wind blast and to rapid deceleration. It has been stated that a wind blast of 500 miles per hour will cause severe physical injury and therefore, ejection at that, or greater, speed is not practicable. It is of interest that the original experiments on the effect of wind blast on human subjects were performed by the Germans. In this country only a small number of humans have been exposed to high velocity wind blasts in wind tunnels, but the results have definitely indicated the seriousness of the problem. It appears, therefore, that some protection to wind blast must be afforded the pilot until sufficient deceleration has taken place and the air speed reduced. In consequence, considerable thought is being given to the production of a detachable cockpit which will afford the desired protection from wind blast and from which the pilot may safely escape for a normal parachute descent after the effects of initial deceleration have sufficiently diminished.

The speed at which our modern planes will perform introduces the problem of acceleration. In this discussion, we will not consider lineal or angular accelerations but will confine our remarks to acceleration of the radial type which is produced by change in direction of motion.

If a plane, flying a straight course, is turned to the right or left, the pilot is subjected to a force acting in the opposite direction from the center of the arc of the turn. The intensity of the force depends on the speed of the aircraft and the radius of the turn. The unit used in the measurement of this force is that of the pull of gravity and hence is designated as "G."

It is, of course, obvious that both plane and pilot are subjected to the same force and that the performance of each is limited by the ability to withstand that force. The builder of an airplane, knowing the purpose for which the plane is to be used and knowing the maneuvers through which his plane is to be put, can calculate the forces which will ensue and can build his plane to withstand those forces. Unfortunately, we cannot rebuild the human body and our best efforts so far have not yet succeeded in increasing human tolerance to radial acceleration to any radical degree.

There has been developed a suit equipped with expansible bladders which inflate automatically when "G" forces are applied to the pilot and which by reinforcement of certain body areas will positively increase the human tolerance. The suit was used during the war and definitely improved the performance of fighter pilots by permitting more radical maneuvers of planes but the increased protection afforded was a matter of but approximately one and five-tenths "G." The wearing of these suits during combat or acrobatic flights also produced an unlooked for secondary result in that there was a definite diminution of fatigue. This effect was very marked and was no small factor in popularizing the suits. The cause of production of fatigue as

a result of exposure to the forces of acceleration is unknown and requires further investigation.

The last point under discussion is the question of the effect of sound waves on the human body. We are all familiar with the effect of audible sound waves on the ear and know that hearing can be reduced as the result of exposure to excessive sound intensities. However, we are not so well informed as to the effects of sound on other body structures, nor do we have knowledge of the effects of exposure to sound waves whose frequencies are below or above the audible limits. Once again the Germans were the first to appreciate the importance of investigating the physiological effects of these sound waves, probably because of their early interest in jet engines and rockets. Their work, however, was far from conclusive and was not sufficiently advanced to be of much value.

In this country investigations are underway in the field of vibration stimulated by our own use of jet engines. We have evidence to indicate that inaudible vibration waves can produce symptoms, but to date the research which has been accomplished in this field has not been sufficient to define the frequencies involved nor the physiological disturbances produced. There have been conjectures to the effect that higher frequencies, of perhaps 200,000 cycles and above, if of sufficient intensity, may interfere with reflex or voluntary actions and may even produce mental confusion. These are conjectures, however, and have not been supported by scientific experiments. Obviously, the field of investigation is a broad one and will require extensive research.

As stated before, our high performance aircraft are attaining speeds which are approaching the speed of sound. The closer such speed is neared, the more critical becomes our need to know the physiological limitations of the human pilot. The major efforts of Aviation Medicine are concentrated on that problem.

DILUTION ACIDOSIS *

By GEORGE T. SHIRES † and JAMES HOLMAN,‡ M.D., *Dallas, Texas*

IN studying the effects of rapid saline administration upon circulation and respiration in the dog, a constant and progressive acidosis of arterial blood has been noticed. This effect has been noticed by Odaiva,¹ Essen,² Skelton,³ and Van Slyke,⁴ but apparently this concept has not been advanced or recognized in the recent literature. Since it is a very common hospital practice for physicians to administer isotonic sodium chloride (.9 per cent NaCl) intravenously in many disease states, it was thought worthwhile to report the effect and action of this administration upon blood pH. This administration is an attempt on the part of the physician to maintain proper electrolyte, fluid, and acid-base balance, or to correct disturbances in these vital body equilibria. However, adverse effects may be obtained if saline administration is carried out during unfavorable conditions or when administered in excess.

It can be demonstrated in vitro that if one adds some neutral fluid, such as .9 per cent NaCl, to a buffer solution containing 28 millimols per liter of total bicarbonate with a 1:20 ratio of $\text{H}_2\text{CO}_3/\text{NaHCO}_3$, although the total buffering capacity per unit volume is lowered, the pH is not altered because the ratio of acid to salt remains constant. Assuming then that the total amount of NaHCO_3 in the body is approximately 28 millimols per liter—as measured by the total blood CO_2 —and that there is a normal 1:20 relationship of $\text{H}_2\text{CO}_3/\text{NaHCO}_3$, it is readily apparent that dilution of this buffer system by some fluid such as .9 per cent NaCl would simply decrease the buffering power of the system, but as long as the 1:20 ratio remained constant there would be no change in pH. Since, however, there is a constant production of CO_2 by the body tissues, it is readily seen that the H_2CO_3 numerator remains constant, and it is actually the denominator which is diluted. This will change the pH of the blood buffer toward acidity, since the ratio has been seriously altered. Such a state has been termed dilution acidosis by Van Slyke.⁵

A demonstration of this effect in the intact dog has been carried out in the following manner.

(1) Dogs were anesthetized with nembutal. One femoral vein was opened for administration of .9 per cent NaCl, and one femoral artery cannulated for removal of arterial blood samples, upon which pH was determined by the Coleman pH electrometer (glass electrode method), and total CO_2 content by the method of Van Slyke and Neill.

(2) Nine-tenths per cent sodium chloride was given intravenously at

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From the Department of Internal Medicine, Southwestern Medical College, Dallas, Texas.

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the rate of 300 cubic centimeters per minute, with the results shown in figure 1 (a rather remarkable drop in pH from 7.55 to 7.21, the total CO_2 content of arterial blood decreasing from 49.6 volumes per cent to 31.9 volumes per cent). In all probability the flattening of the curve in figure 1 was due to a partial adjustment toward alkalinity consequent to limitation of CO_2 as a result of respiratory stimulation from (a) marked, rapid decrease in blood pH⁶ and (b) increase in venous pressure as a result of increase in blood volume.^{7, 8} However, this effect may have been due, in part, to the fact that

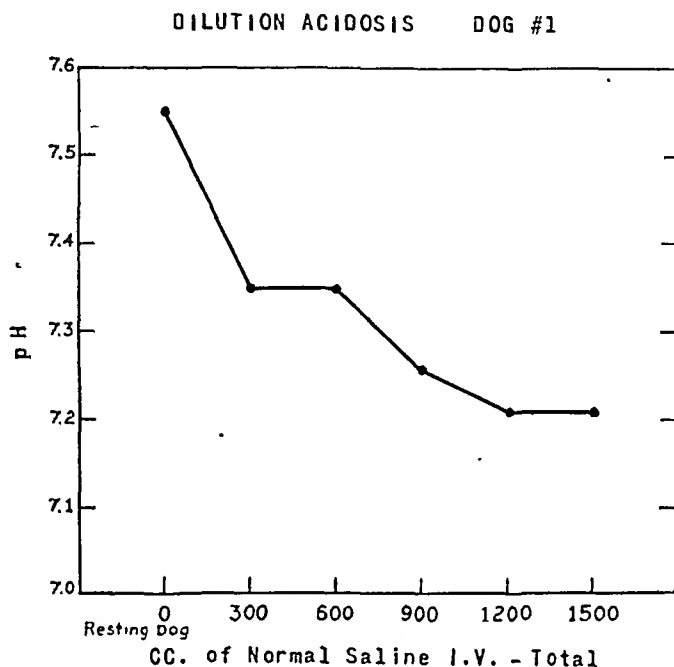


FIG. 1.

blood was diluted to its maximum extent in the first few minutes of the experiment, and the flattening represents beginning dilution of extracellular fluid in the body tissues.

As a control experiment, commercially available balanced saline-bicarbonate solution (containing 6.44 gm. NaCl , 2.52 gm. NaHCO_3 , and .18 gm. KCl per liter which is sold commercially by the Upjohn Company under the trade name of "isonate") was administered in the same manner as described above for the dogs in which saline was used. It is readily apparent, from figure 2, that the total millimols per liter was not exactly the same in this solution (prepared for human use) as in the dogs; nevertheless, once equilibrium was reached, the same amount of fluid could be given in a similar period of time as was saline with a rise in total CO_2 content of arterial blood from 47.2 volumes per cent to 55.8 volumes per cent, without any alteration of pH.

This seems to be evidence that dilution of total body base can occur with saline administration, and that this can be prevented by giving a significant amount of NaHCO_3 , simultaneously. Granting that this is a rather large

amount of fluid per unit of body weight and rather rapid administration, it is obvious that this principle may be of importance in fluid therapy such as:

- (1) Extremely rapid administration of saline to a patient for any cause.
- (2) Diabetic acidosis (remembering that in acidotic states any further decrease in alkaline reserve is likely to have adverse effects).

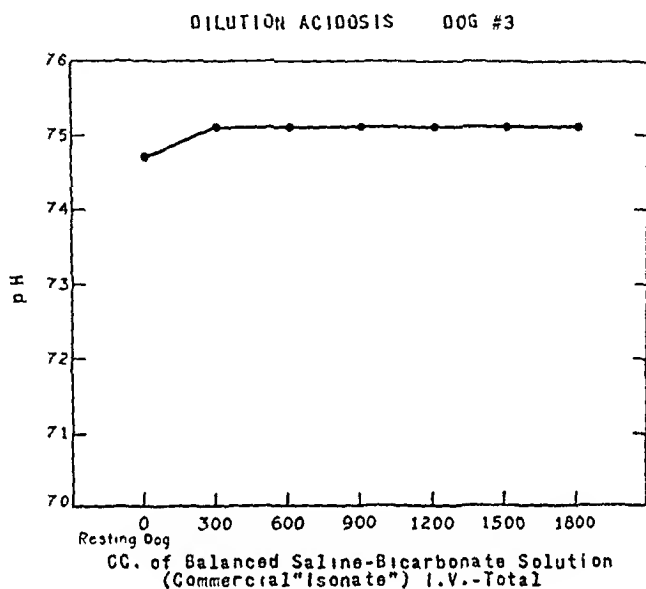


FIG. 2.

(3) Since the kidney normally will sacrifice water volume to conserve proper electrolyte concentration, any condition in which there is marked renal damage, characterized by inability to excrete electrolytes properly, will increase the tendency toward dilution acidosis. Among the conditions which may cause such a tendency are certain instances of structural damage to the kidney, and also renal circulatory disturbances from any cause.

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FUNCTIONAL PATTERNS IN RENAL DISEASE*

By A. C. CORCORAN, R. D. TAYLOR, F.A.C.P., and IRVINE H. PAGE,
F.A.C.P., *Cleveland, Ohio*

THE introduction of procedures by Homer Smith which permit the measurement of minimal renal blood and plasma flow, glomerular filtration rate and tubular secretory capacity has enabled measurement of renal function in terms which are functional rather than empirical. The validity of interpretations based on these methods is not seriously questioned when they are applied to the study of changes in the function of normal kidneys. Certain reservations need to be introduced in the presence of renal damage. Nevertheless, observation of changes of renal function and circulation in disease by these methods tends to reveal the nature and extent of the underlying structural changes. The patterns thus provided may support or extend a clinical diagnosis and give an objective basis for prognosis.

The purpose of this report is to review from this aspect observations made by these methods in various diseases affecting renal function. From this review of data we shall indicate the functional patterns of several forms of renal disease, and consider their relationship to concurrent structural and clinical change.

PROCEDURES

Most of the observations were made in the ward of the Lilly Laboratory for Clinical Research, Indianapolis City Hospital. The measurements made include (1) plasma diodrast clearance at low plasma concentrations, (2) plasma inulin clearance, and (3) tubular secretory capacity for diodrast (T_{mD}). Other observations include determination of hematocrit index, plasma total protein content and arterial pressure during the test. The methods used have been described in previous reports. Some of the observations were made at the Research Division of the Cleveland Clinic Foundation. The functions measured in these instances were (1) plasma p-aminohippurate (PAH) clearance at low plasma concentrations, (2) plasma inulin clearance, and (3) tubular secretory capacity for p-aminohippurate (T_{mPAH}). In some patients of the Cleveland group, the estimate of glomerular filtration rate was made from the plasma clearance of mannitol.[†] To facilitate comparison of these observations with those in which diodrast and inulin were used, we have (a) estimated probable T_{mD} from measured T_{mPAH} by dividing the latter by the factor 1.8 (Chasis, Redish, Goldring, Ranges, and Smith,¹ 1945) and (b) have made allowance for the tubular

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From the Research Division of the Cleveland Clinic Foundation, Cleveland, Ohio.

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reabsorption of mannitol (Berger, Farber and Earle,² 1947; Corcoran and Page,³ 1947; Smith, H. W.,⁴ 1947; and Hoobler,⁵ 1947) by dividing measured plasma mannitol clearance by the factor 0.9. We have noted in the data where these factors are applied.

Plasma clearances of diodrast or of p-aminohippurate (PAH) at low plasma concentrations are accepted as equivalent to minimal renal plasma flow (RPF) from which minimal renal blood flow (RBF) is calculated using the venous hematocrit index. Plasma inulin clearance is taken as equivalent to the rate of glomerular filtration (GFR). Secretory T_m , the maximum tubular secretory capacity for either diodrast or p-aminohippurate, is a tubular function which, in most circumstances, is taken as measuring the mass of functioning tubular tissue. Reservations in interpretations of these functions in specific diseases are noted in the text. Plasma clearances, T_{mD} and arterial pressure, recorded as P_m (mean of systolic and diastolic brachial pressures) constitute the *direct* observations.

The *derived* data are the clearance ratios and calculated resistances. The ratios are (a) inulin/diodrast or filtration fraction, abbreviated as FF; (b) calculated renal blood flow per unit T_{mD} , abbreviated as RBF/T_{mD} and (c) inulin clearance per unit T_{mD} , abbreviated as GFR/T_{mD} . Filtration fraction measures the proportion of water filtered per unit plasma flow. It varies with effective filtration pressure, assuming the glomeruli to be intact. RBF/T_{mD} measures the rate of blood flow per unit T_{mD} and, in most circumstances, is taken as indicating blood flow of functioning tissue. GFR/T_{mD} measures the rate of filtration per unit secretory capacity. A change in this ratio from the normal is indicative of a change from the normal balance of glomerular and tubular functional activity.

The procedure suggested by Lampert⁶ (1941) is used in calculating apparent renal vascular resistance. This method expresses as R_A (afferent resistance) the resistance to the flow of blood in the afferent tract from aorta to the end of the glomerular capillaries. R_E (efferent resistance) is the resistance from the end of the glomerular capillaries to the peritubular capillaries and is principally expressive of the resistance of the efferent arterioles. The sum of these two resistances, R is taken as measuring total renal arterial arteriolar resistance.

The text of this report is divided into eight categories of renal disease. Relevant data are provided or sources indicated. The pattern characteristic of the condition is then described with its probable mechanism. Comparison with other conditions and specific comments complete these discussions. Finally, the eight patterns are exemplified and compared, demonstrating the large degree in which they reveal underlying structural and functional disorders.

I. HYPERTENSIVE VASCULAR DISEASE (ESSENTIAL HYPERTENSION)

Our largest interest in and experience with these methods concerns their use in essential hypertension. This disease principally involves arterioles.

The renal arteriolar bed includes two sets of arterioles and since the kidneys normally receive 20 per cent of the cardiac output, it is to be expected that tests which measure hemodynamic changes will have an especial application in this disease.

(a) *Classification.* Essential Hypertension. This state is defined as one of persistent elevation of diastolic and systolic arterial pressures due to unknown causes and characterized by the presence of increased peripheral resistance due principally to arteriolar constriction and an increased cardiac effort.

Essential hypertension can, on clinical grounds, be variously subdivided (Page and Corcoran,⁷ 1945). What seems to us a satisfactory grouping consists in viewing the process as occurring in three aspects or phases.

The first of these may be termed *early essential hypertension*. It is early in the sense that the basic process has not advanced to the point of causing or being associated with definite and serious vascular injury. It is not necessarily early in point of time, since this state may persist for several years. It is characterized by moderate, widely fluctuant, sometimes remitting increases of arterial pressures. These are associated with no more than minimal evidences of arteriovascular disease, renal or extra-renal. Most of the patients in whom the *early* phase persists for long periods show signs of disordered central nervous activity, either as the diencephalic syndrome (Page,²² 1935) or as emotional difficulties which try the patience of their families, physicians and themselves. The coincidence in these of a lack of emotional balance with a disease process which is predominantly functional and which causes little or no progressive damage is the basis for terming the condition "neurogenic." The presumption is that the disease is based on disordered vasomotor function.

The second phase, that of *established essential hypertension*, is characterized by evidences of failure of some part of the cardiovascular system to adjust to and maintain itself against the stress of the disease. During this phase the increases of pressure are somewhat more marked than in the former groups, and less remittent. The vascular injury is slowly progressive.

The third aspect of essential hypertension is *malignant hypertension*. It is characterized clinically by evidences of rapidly progressing arterial and arteriolar damage in the form of retinopathy (papilledema, hemorrhages, and exudates). It is often associated with weight loss, hematuria, moderate proteinuria and disabilities of cardiac or cerebro-vascular origin. Such patients at autopsy reveal necrotizing arteriolitis, a more intense arteriolar sclerosis than is present in the former group. The anatomical diagnosis is usually malignant nephrosclerosis, a term which we consider inapposite since, the clinical process is often severe in extra-renal structure and may occur when renal function and structure are presumably well preserved.

The relationship of these aspects of essential hypertension to each other will be the topic of another report.

Anatomically and functionally, *arteriosclerotic hypertension* is distinct from any of the aspects of essential hypertension. However, for convenience in comparison, data from patients suffering from arteriosclerotic hypertension will be considered together with those of patients suffering from essential hypertension. Arteriosclerotic hypertension is characterized by a predominantly, often exclusively, systolic increase of arterial pressure. The condition usually has its onset at about age 50. It is only slowly progressive. A constant clinical characteristic of this condition is the tendency of arterial pressure to be widely variable and decrease to or towards normal levels during bed rest, presumably as the result of a decreased cardiac output. Functionally, the increase of systolic pressure is the result of a decreased elasticity of the aorta and greater elastic arteries.

It will be observed that the above grouping of patients is clinical. It is made without reference to data on renal function. Consequently the renal function pattern in each sub-group will reveal the correlation of quantitative changes of renal function with the clinical estimates of the nature and severity of the disease process.

(b) *Extra-renal Findings.* The number studied in each clinical group, the distribution by sex, mean age in years, mean estimated duration of hypertension, mean estimated severity of extra-renal vascular disease and the number of patients dying during the period of observation (mean interval three years) is shown in table 1. The estimate of duration of disease

TABLE I
Grouping of Patients Suffering from Essential Hypertension and
Arteriosclerotic Hypertension

Group	Num- ber of Pa- tients	Male	Female	Years		Extra-Renal Disease			Died Num- ber	Number Fol- lowed
				Duration Average	Age Average	C.	H.	E.		
Early total	32	20	12	7	32	0.2	0.1	0.6	0	32
(a) E-R-V damage present	17	12	5	6.6	29	0	0	0	0	17
(b) E-R-V damage absent	15	8	7	7.7	35	0.4	0.2	1.3	1	15
Established	76	42	34	10.7	45	1.3	1.1	2.1	23	75
								V R		
Malignant	58	40	18	8.2	42	1.9	1.2	3.0	49	55
Arteriosclerotic	17	10	7	4.6	56	0.8	0.7	1.9	1	17

Distribution of patients with hypertension by, column (1) number examined, (2) and (3) sex, (4) average duration of disease and (5) average age. The severity of extrarenal vascular disease was estimated arbitrarily as 1 to 4+: averages for such disease in cerebral (C), heart (H) and eyegrounds (E) are shown. The latter panel is subdivided into V—representing vessels and R—representing retina, in the cases of malignant hypertension and arteriosclerotic hypertension. The period of observation averaged three years for the whole group. The number dying and number followed are indicated in columns (7) and (8). It should be added that the patient dying during observation in the early group succumbed to coronary occlusion and myocardial infarction; the one dying in the arteriosclerotic group was fatally injured in an accident. The mean duration of symptoms of malignant hypertension in this group was three months before observation.

is from the time of our observation back to the first observation of an increase of arterial pressure or to the time of the first sign or symptom of hypertensive disease. The estimates of extra-renal disease are made in three categories. These are category C, which refers to the degree of cardiac damage or strain as estimated from symptoms and from the electrocardiogram, category H, which estimates the degree of cerebrovascular disease from symptoms and signs (Taylor and Page,⁸ 1945) and category E, which estimates the degree of vascular injury shown in the fundoscopic examination. The latter category is subdivided, in the case of malignant hypertension, into sub categories as V (for vessels) indicating vasoconstriction and sclerosis and F (for

TABLE IIa
Summary: Renal Functional Data in Hypertension
(a) Direct Observations

Function		Normal	Early	Established	Malignant	Arteriosclerotic
R.B.F. c.c. per 1.73 M ²	Mean	1075	1153	697	369	710
	S.D.	±233	±196	±218	±228	±274
	100 S.D./M.	21.6	17	31	62	39
	Range		788-1662	298-1235	75-1053	393-1042
R.P.F. c.c. per 1.73 M ²	M.	674	630	393	216	407
	S.D.	±128	±109	±115	±135	±101
	100 S.D./M.	19	17	29	62	25
	Range		469-890	178-670	47-564	220-584
GFR c.c. per 1.73 M ²	M.	128	130	93	61	89
	S.D.	±20.2	+22.8	+25.3	±31.7	±29.5
	100 S.D./M.	16	-17	27	52	33
	Range		77-192	44-176	15-137	47-124
Tmp mg. I per 1.73 M ²	M.	49.4	47.5	36.4	21.3	35
	S.D.	±8.8	±5.5	±5.8	±11	±7.9
	100 S.D./M.		12	16	51	22
	Range		36-62	19-55	4.5-43	21-51
Pm mm. Hg	M.	100	126	154	176	134
	S.D.		±16.2	±19	±17.8	23
	100 S.D./M.		12	12	10	17
	Range		98-165	110-200	134-213	98-180

fundus) estimating the degree of retinopathy. All estimates are made on the basis of + to +++++.

Comments. In table 1, the group of early hypertension is subdivided according as extra-renal vascular damage is present or absent. The mean age of the patients in this group who show no evidence of extra-renal vascular damage is younger than that of patients who show some changes. However, neither this difference nor the apparent difference in duration of the disease, between these two sub-groups is statistically significant (difference/standard error of the difference less than 2). Similarly, the renal functional status of the patients in the two sub-groups of *early hypertension* is identical. Consequently, this subdivision is disregarded in the discussion of renal function which follows.

The male sex is preponderant in all groups. Mean age of patients with *established essential hypertension* is 10 years greater than that of patients with *early essential hypertension*. This difference is significant (difference/standard error of the difference = 6.7). The mean age of the group with *established essential hypertension* is greater than that of the group with *malignant hypertension*, but the difference is not statistically significant. The

TABLE IIb
Summary: Renal Functional Data in Hypertension
(b) Derived Values

Function		Normal	Early	Established	Malignant	Arteriosclerotic
FF	Mean S.D. 100 S.D./M. Range	0.19 +0.024 13	0.205 ±0.05 24 0.15-0.29	0.241 ±0.051 21 0.13-0.35	0.29 ±0.04 14 0.20-0.44	0.225 ±0.06 27 0.16-0.28
RBF/T _{MD}	Mean S.D. 100 S.D./M. Range	23.78 ±3.65 15	24.60 ±4.16 17 17.6-34.7	19.70 ±5.61 29 13.2-32	16.98 ±5.57 33 9.46-32.8	21.0 ±4.67 22 14.9-29.2
GFR/T _{MD}	Mean S.D. 100 S.D./M. Range	2.68 ±0.402	2.75 ±0.42 15	2.66 ±0.67 25	2.95 0.56 19	2.52 ±0.38 15
R _A	Mean S.D. 100 S.D./M. Range	1.12	1.75 0.4-4.0	3.75 0.8-8.3	5.65 2.6-10.9	2.52 1.64-5.26
R _E	Mean S.D. 100 S.D./M. Range	1.04	0.85 0.5-1.37	1.38 0.5-4.06	1.60 0.7-3.2	1.06 0.6-1.44
R	M. S.D. 100 S.D./M. Range	2.16	2.85 ±0.89 31 1.55-5.98	5.11 ±1.81 35 1.37-12.4	7.16 ±2.5 35 3.36-12.6	3.54 ±1.02 29 2.4-6.56

Means, standard deviations (S.D.), coefficients of variation (100 S.D./mean) and range of observations in patients suffering from hypertension. R.B.F. = minimal renal blood flow; R.P.F. = minimal renal plasma flow; G.F.R. = glomerular filtration rate; T_{MD} = maximum tubular secretory capacity for diodrast in mg. iodine; all corrected to 1.73 sq. meters body surface. P_m = average arterial pressure as mean of systolic and diastolic in mm. Hg. R_A = afferent arteriolar resistance, R_E = efferent resistance and R = total resistance (R_A + R_E) in mm. Hg per c.c. of blood flow per unit T_{MD}. These symbols have the same significance in subsequent tables.

group with *arteriosclerotic hypertension* is significantly older than the *established essential* group.

From the estimate of duration, the onset of disease in the *early* group would occur at mean age 25 and in the patients with *established essential hypertension* at mean age 34. This difference and the similar difference when the comparison is made with the patients who suffer from *malignant hypertension* are probably artefacts which reflect the greater frequency of

observations of arterial pressure in recent years. If this explanation is granted, it seems likely that the brief duration of hypertension in the *arteriosclerotic* group is accurately estimated.

(c) *Renal Function.* The observations with which the data are composed were made at the time the patient first came under observation. Because of the large number of observations, the data are presented as a statistical summary. Observations made during some reversible states such as cardiac failure are excluded. Means, standard deviation [$S.D. = \sqrt{\Sigma/(n-1)}$], coefficients of variability (100 $S.D./\text{mean}$) and the range of variation are listed. The direct observations from plasma clearances and arterial pressure are presented in table 2a. Values derived from these (derived data) are collected in table 2b. In both tables the comparison is made by clinical groups with data from normal subjects.

Early Essential Hypertension. Means of direct observations with the exception of arterial pressure are well within the range of data from normal

TABLE III
Renal Function in Cushing's Syndrome

No.	RBF	RPF	GFR	T _{mp} mg.	Pm	FF	RBF/T _{mp}	GFR/T _{mp}	R _A	R _E	R
	c.c. per 1.73 sq. m./min.						c.c./min.				
1	687	374	77	39.9	—	0.21	17.2	1.92	—	—	—
2	495	271	77+	32.2+	135	0.28	15.4	2.38	3.78	1.42	5.20
3	518	295	71	27.8+	120	0.24	18.6	2.54	2.05	1.24	3.33
4	446	201	71+	26.7+	140	0.35	16.7	2.66	2.82	1.95	4.77
5	463	278	59+	19.6+	122	0.21	23.6	3.0	2.48	0.64	3.12

subjects. Among the derived data (table 3) only R_A and R are increased. In this condition, then, there is usually normal renal blood flow, glomerular filtration rate and tubular secretory activity, but an increase in vascular resistance in the afferent tract which accounts for an increase in renal resistance. Variability of FF is greater than in normal subjects.

Established Essential Hypertension. Mean values of the direct observations are definitely abnormal (table 2a). The ratios to the normal of the means are as follows: $RBF = 0.65$, $RPF = 0.58$, $GFR = 0.73$, $T_{mD} = 0.73$, P_m (mean of systolic and diastolic brachial arterial pressures) = 1.5. Means of derived values other than GFR/T_{mD} are similarly abnormal. The ratios of these to the normal are $FF = 1.27$, $RBF/T_{mD} = 0.83$, $GFR/T_{mD} = 0.99$, $R_A = 3.3$, $R_E = 1.3$, $R = 2.3$. Many values observed in patients of this group extend into the range observed in patients with *early essential hypertension* and in normal subjects. However, the average pattern is one of loss of tubular secretory capacity, a more extensive depression of blood and plasma flow, a less severe decrease of glomerular filtration, and increase of FF. The increased resistances, both afferent and efferent, lead to reduction of renal blood flow to the residue of tubular tissue.

Malignant Hypertension. Means of direct observations are still more abnormal than in the last group. The ratios of change from the normal are as follows: $RBF = 0.34$, $RPF = 0.32$, $GFR = 0.48$, $T_{MD} = 0.43$, $P_m = 1.7$. Means of derived values other than GFR/T_{MD} are grossly abnormal, their ratios to normal being $FF = 1.5$, $RBF/T_{MD} = 0.7$, $GFR/T_{MD} = 1.1$, $R_A = 5.1$, $R_E = 1.5$ and $R = 3.3$. Even in this phase a few patients yield some values which are not significantly abnormal. But the mean pattern is an exaggeration of the changes seen in the preceding group.

COMMENT

Early Essential Hypertension. The normal values for all functions other than renal resistance demonstrate that renal ischemia is not the cause of hypertension in this phase and indicate that the initial renal vascular change is constriction of afferent arterioles. Comparison of the renal functional states of such patients with those in other groups indicate the renal parenchymal damage in the other groups is a sequel to rather than a cause of essential hypertension. It should be noted that the absence of renal functional abnormality in these tests is not evidence of an extra-renal origin of the hypertensive disease, since experimental renal hypertension can be produced in dogs without demonstrable or lasting impairment of excretory function (Corcoran and Page,⁹ 1942).

The 33 per cent increase in renal resistance present in these patients affects 20 per cent of the cardiac output. The concurrent increase in total peripheral resistance may be estimated at 25 per cent. The renal arteriolar constriction present in these patients therefore accounts for 30 per cent of the increase in total peripheral resistance.

Finally, variability of some functions in this group as contrasted with normal subjects testifies to the occurrence in the renal vascular bed of the vasomotor instability so characteristic of early essential hypertension.

Established Essential Hypertension. The reduction of blood flow, filtration and tubular secretory capacity indicates a loss of tissue or at least a suspension of function. Assuming, as seems likely, that the decrease in T_{MD} is due largely to loss of nephrons, this loss is found to average 27 per cent. It is associated with a proportionate decrease in glomerular filtration rate. The reduction in these functions is presumably due to arteriosclerotic obliteration with focal ischemic atrophy. The mean reduction in minimal renal blood flow is greater proportionately than the changes in T_{MD} and filtration. The secreting tissue which remains in function is therefore ischemic, since it is receiving on the average only 83 per cent of its normal quota of blood. Since glomerular filtrate is squeezed from the plasma by hydrostatic pressure, it follows also that glomerular filtration pressure is increased. These changes are associated with increases in renal resistances, afferent and efferent. The increase in efferent resistance is probably due to vasoconstriction, since this arteriole is rarely sclerotic. The increase in

afferent resistance is attributed to the summation of afferent arteriolar constriction with arteriolar sclerosis.

Alternative explanations of some of these changes have been proposed (Smith,¹⁰ 1941; Goldring and Chasis¹¹; Findley, Edwards, Clinton and White,¹² 1942). In these it is assumed that the kidney in hypertension suffers specific injuries which alter the normal interpretation of changes in the clearance pattern. Evidences of such injury have been demonstrated in some patients (Smith,¹³ 1943). However, since the interpretation proposed here is consistent with what is known of the anatomical and functional changes present in *established essential* hypertension, we believe that it will apply to most patients.

The contribution of renal vascular resistance in functioning areas to total peripheral resistance in this phase of the disease can be estimated as 20 per cent.

Malignant Hypertension. In this stage there is on the average nearly twice as much loss of T_{MD}, presumably due to loss of tubular tissue, as was present in *established essential hypertension*. The tissue remaining in function receives only 70 per cent of its normal blood flow. Renal vascular resistance is increased to a greater degree than in the former group. The increase of resistance and greater loss of tissue testify to the greater severity of renal vascular injury, both constrictive and sclerotic, present in malignant hypertension as compared with established essential hypertension.

The values in some patients extend into the normal range, but in most these values, which are our first observations in these patients, testify to a process which is already far advanced. The skewed scatter of data testifies to the rapidity of renal functional deterioration. Most of these patients are first seen only when renal damage is severe.

Arteriosclerotic Hypertension. The pattern resembles in most respects that seen in *established essential hypertension*. The difference consists in the fact that the increase in vascular resistance in functioning areas is predominantly afferent. The coincidence of afferent resistance with tissue loss speaks for an obstructive rather than vasoconstrictive lesion and accords with the structural and functional changes underlying *arteriosclerotic hypertension*. Functional data do not indicate the focus of the obliterative afferent renal vascular lesions. Anatomical data show that it affects larger arterial channels, rather than the arterioles which are affected in essential hypertension.

Summary. The renal functional pattern in *early essential hypertension* is that of a condition which is functional, in which there is neither renal ischemia nor loss of nephrons and in which vasoconstriction extends only to the afferent arteriole. In the phase of *established essential hypertension*, arteriolar sclerosis is present with consequent renal structural loss. There is vasoconstriction of afferent and efferent arterioles, and, usually, some ischemia of the tubular areas remaining in function. Glomerular filtration pressure is increased. In *malignant hypertension* the changes present in

the established essential phase are greatly exaggerated. The average pattern is one of severe structural loss with severe arteriolar sclerosis and constriction of arterioles, ischemia of the tissue remaining in function and a marked increase in glomerular filtration pressure. Since some of the observations extend into the normal range and many into the range observed in the phase of established essential hypertension, it is evident that the syndrome of malignant hypertension is not the result of renal excretory insufficiency. Rather, the spread of the data indicates that it is a process which is characterized by a rapidly progressive renal vascular damage. *Arteriosclerotic hypertension* reveals a pattern consistent with obliterative lesions of afferent arteries or arterioles which does not usually result in a severe loss of renal function and in which vasoconstriction is presumably absent. The demonstration that similar renal functional patterns occur in old age in the absence of hypertension (Shock,²³ 1946) does not militate against this interpretation.

Most of these conclusions find support in the data of former writers (Chesley and Chesley,¹⁴ 1940; Friedman, Selzer and Rosenblum,¹⁵ 1941; Foa, Woods and Peet,¹⁶ 1942; Steinitz,¹⁷ 1941; Talbott, Castleman, Smithwick, Melville and Pecora,¹⁸ 1943; and Hilden,¹⁹ 1946; and others).

II. OTHER DISORDERS ASSOCIATED WITH ARTERIAL HYPERTENSION

(a) *Cushing's Syndrome*. Observations were made in one male and three female adults referred by Dr. E. P. McCullagh. These presented the typical clinical pattern of Cushing's syndrome. All showed systolic and diastolic arterial hypertension, and their retinal arterioles revealed constriction and sclerosis.

The results of tests of renal function are shown in table 3 in which is included an observation made by Barnett, Perley and Heinbecker²⁰ (1943) in an adult suffering from this condition (No. 1). The renal functional pattern is similar to that of established essential hypertension. In our four patients the levels of RBF are relatively uniform and lie well below the mean found in our group of *established essential hypertension*, as does also the mean of Tmp. In the observation cited from Barnett, Perley and Heinbecker, the levels of function are higher. The pattern in our patients is one which testifies to loss of renal tissue as the result of obliterative arterial and arteriolar disease, associated with constriction of the afferent and efferent arterioles in functioning areas.

It is tempting to attribute the renal vascular lesion in this condition to nephrosclerosis resulting from excess of cortical steroids, to draw an analogy of the lesion produced in animals by administration of large doses of desoxycorticosterone (Selye,²¹ 1946) and to consider the arterial hypertension as due to stimulation of renal pressor activity consequent on nephrosclerosis. That this is the mechanism of the renal injury and the hypertensive disease in Cushing's syndrome is far from established. But, assuming the analogy to be exact, restriction of sodium and administration of ammonium salts is

indicated as a means of retarding the progress of the lesion. The comparatively low levels of renal function found in our patients with Cushing's syndrome testifies to the importance of the renal lesion in this condition and the desirability of controlling its spread.

(b) *Pyelonephritis* (table 4). Observations were made in five patients in whom chronic pyelonephritis was associated with arterial hypertension and in two patients whose levels of renal function lie in the same range, but in whom arterial pressure was normal. The renal lesion was not *acutely active* in any one of these patients at the time of observation. For the sake of

TABLE IV
Renal Function during Chronic Pyelonephritis

No.	RBF	RPF	GFR	Tm _D	Pm	FF	RBF/Tm _D	GFR/Tm _D	R _A	R _B	R
	c.c. per 1.73 sq. m./min. mg.						c.c./min.				
(1) With Arterial Hypertension											
6-10 (av.)	689	409	96	38.2	160	0.23	18.0	2.50	4.56	1.24	5.80
(2) Normotensive Inactive											
11-12 (av.)	413	249	50	22.5	107	0.20	184	2.20	1.16	1.11	2.27
(3) Active											
13	433	316	39.5	12.8+	100	0.12	33.6	3.09	—	—	—
14	409	262	29.3	11.3+	136	0.11	36.2	2.60	—	—	—

comparison, then, we have included in table 5b observations made in two patients suffering from chronic pyelonephritis in whom the process was active (as evidenced by fever, leukocytosis, pyuria, tenderness over the renal areas) at the time of observation.

The functional pattern in the patients in whom pyelonephritis is associated with hypertension is nearly identical with that present in established essential hypertension. The pattern in the two normotensive patients in remission is one of simple loss of function. In the patients in whom the renal inflammatory reaction was *acutely active* at the time of observation, the levels of filtration rate and fraction are greatly reduced and RBF/Tm_D increased. The changes in other functions are consistent with simple loss of tissue.

The functions of tubular secretory capacity, renal blood flow and glomerular filtration rate were decreased in all the observations. The loss of tissue in the normotensive patients must be taken as a result of the inflammatory process. It is therefore likely that inflammatory injury as well as arteriovascular disease participated in reducing function in the groups in

whom hypertension is present. In contrast to the findings in the normotensive patients in whom the disease is inactive, the decrease of filtration rate and fraction in the patient with an active lesion suggest that there is a decrease in effective filtration pressure. A decrease in filtration pressure might result from increased renal interstitial pressure consequent on the inflammatory reaction. However, the increase in RBF/T_{md} during the active phase suggests that there is a loss of tubular secretory capacity which is out of proportion to the level of RFF and presumably CFR. This abnormality is seen also in diffuse glomerulonephritis (see below).

TABLE V
(a) Acute Diffuse Glomerulonephritis

No.	RBF	RPF	GFR	T _{md}	Pm	FF	RBF/T _{md}	R _A	R _E	R	GFR/T _{md}	T.P.
1	1544	857	110	64	100	0.13	24.3	1.25	0.65	1.90	1.72	6.9
2	1478	872	103	36	95	0.12	41.2				2.93	8.2
3	1328	784	123	43	87	0.16	30.9	0.65	0.48	1.13	3.1	6.1
4	1192	668	69	26	95	0.10	46.0	0.78	0.26	1.04	2.7	5.5
5	765	507	49	39	95	0.10	19.4	1.25	0.72	1.97	1.26	6.9
6	652	437	59	25	110	0.14	26.0	1.87	0.52	2.4	2.35	6.6
7	413	272	22	91	120	0.08	45.0	1.38	0.25	1.6	2.4	6.1
8	263	173	17	4.0+	105	0.10	66.0	0.84	0.08	0.96	4.25	5.5
9	235	143	21+	4.2+	133	0.15	56.0	1.30	0.24	1.54	4.85	5.0

Healing Stage

3	1065	628	113	48	92	0.18	22.2	1.10	0.72	1.85	2.35	6.1
5	1007	689	124	55	91	0.18	18.3	1.15	0.90	2.05	2.25	7.0
6	722	419	85	33	112	0.20	22	1.42	0.97	2.37	2.57	7.6
7	718	424	92	365	80	0.22	19.7	0.52	0.89	1.41	2.51	5.9

(b) Chronic Diffuse Glomerulonephritis (Pre-Terminal)

No.	RBF	RPF	GFR	T _{md}	Pm	FF	RBF/T _{md}	R _A	R _E	R	GFR/T _{md}	T.P.
9	1526	938	110	62	116	0.12	24.5	2.5	0.46	2.95	1.78	4.5
10	1172	647	106	43	107	0.16	27.3	1.8	0.47	2.25	2.47	4.6
11	1094	613	83	42+	110	0.14	26.0				1.98	4.2
12	1056	644	116	46	100	0.18	23.0	1.84	0.57	2.41	2.52	5.0
13	980	441	42+	20.4+	114	0.09	48.0				2.06	4.6
14	966	512	85	37	140	0.17	26.1	3.08	0.51	3.59	2.30	5.2
15	951	514	110	36	123	0.21	26.4				3.05	6.6
16	689	658	60	35	129	0.09	25.4	2.89	0.43	3.32	1.72	4.1
17	670	456	70	21	125	0.15	32.0	2.23	0.76	2.99	3.3	4.4
18	589	298	60	28	129	0.20	21.0	2.12	1.06	3.18	2.2	5.9
19	541	360	61	27	110	0.17	20.0	1.87	0.85	2.72	2.2	6.2
20	476	314	42	16	147	0.14	29.7	2.90	0.44	3.34	2.7	5.4
21	256	167	53	26	127	0.32	9.9	5.81	1.96	7.77	2.0	5.1

(c) Terminal Phase (Mean of Observations in 11 Patients)

22-33 (av.) range	80 138- 40	57 97-32	10 19-3	2.3 8.0-0.3	135 123- 157	0.17 0.17- 0.28	34.3 —	—	—	—	4.35 —	6.2 —
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(T.P. = plasma total protein gm./100 c.c.)

From the aspect both of renal functional pattern and clinical impression, the hypertensive disease in the patients in whom hypertension and pyelonephritis are associated is identical with that of well established essential hypertension. The chronic inflammatory renal lesion seems to act as an intra-renal fibrosing equivalent of the extra-renal collagenous reaction of experimental hypertension due to perinephritis (Page,²⁴ 1939). A significant difference lies in the mean age of these five patients, which was 23 years. The presence of established hypertensive disease at an early age may be a clue to the discovery of its source in pyelonephritis.

(c) *Diffuse Glomerulonephritis.* The degree of renal injury in the acute and chronic stages of diffuse glomerulonephritis is so widely variable that an average of observations made in either of these groups can have little meaning or value. The observations in individual patients are presented in table 5. A mean is taken in the 11 patients observed in the terminal stage of chronic glomerulonephritis, when the levels of function are low and comparatively uniform.

Acute Diffuse Glomerulonephritis. The observations in nine patients are listed in table 6a. In these, RBF varies from 1.43 to 0.22 times mean normal; GFR varies from 0.8 to 0.13 times other mean normal and Tmp from 1.27 to 0.08 times mean normal. While direct observations of renal function thus show a wide variation from values which exceed mean normal to low values, glomerular filtration is subnormal in every instance. This

TABLE VI
(a) Intercapillary Glomerulosclerosis

No.	RBF	RPF	GFR	Tmp	Pm	FF	RPF/Tmp	R _A	R _E	R	GFR/Tmp	T.P.
34	1077	657	61	58+	91	0.09	18.6	1.76	0.63	2.4	1.05	5.0
35	946	596	82	26+	135	0.14	36	2.23	0.34	2.6	3.12	4.2
36	609	414	59	21+	130	0.14	29	2.29	0.47	2.76	2.8	5.6
37	477	339	28	18	146	0.08	26	3.2	0.46	3.65	1.56	5.7
38	222	139	25	11+	123	0.18	20	2.77	0.79	3.56	2.28	5.9
39			13	2.7	141						4.8	6.4

(b) Toxic Nephrosis (Vitamin D Intoxication)

40	286	192	37+	10+	137	0.19	28.6	—	—	—	3.7	7.0
41	407	285	48+	12.6+	88	0.17	32.4	—	—	—	3.8	6.0
41 repeat	592	361	93	37	88	0.26	16.0					

(c) Hypotension Due to As₂O₃

42	670	415	34	47	48	0.08	14	—	—	—	0.7	4.7
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Orthostatic Hypotension

43a	376	240	54	18.5	124/85	0.22	20.3				2.82	6
43b	131	87	20	(18.5)	75/62	0.23	7.1				1.07	

depression of glomerular filtration relative to concurrent changes in blood and plasma flow is shown in levels of filtration fraction. This function is depressed in every instance. The average for the group is 0.12.

The increase in the ratio RBF/TmD in seven of nine observations is indicative either of hyperemia in the tissue which remains in function or of a reduction in tubular secretory capacity. The depression of TmD was observed in eight of the nine patients. In these, TmD was either subnormal at the time of the observation, or, if still within the range of normal, was found to increase on healing in the four patients observed in this stage. Thus, depression of TmD is at least a partial explanation of the increase in the function RBF/TmD . That there may be associated with this a true renal hyperemia in acute glomerulonephritis is suggested by the demonstration of an increase in total renal blood flow at the onset of experimental glomerulonephritis in dogs (Fouts, Corcoran and Page,⁵² 1941). Similar renal changes have been shown by Hilden²⁵ (1943) and by Earle, Taggart and Shannon²⁶ (1944).

Thus the apparent renal hyperemia of the residue of functioning renal tissue commonly present in acute glomerulonephritis is probably partly real and partly apparent. The apparent hyperemia (apparent increase in renal blood flow per unit of residual tubular secretory capacity) is termed by Smith¹³ (1943) "vicarious hyperemia," although it seems to us (Corcoran, Taylor and Page,²⁷ 1943) more appropriately termed a "vicarious clearance." It is attributed to secretion by active tubules of material which is not conveyed to them in their own peritubular capillaries but which is diffused in the interstitial fluid from blood which is circulating around inactive tubules. The clearance is vicarious in the sense that the blood is cleared of diodrast or p-amino-hippurate by cells with which it is not in close contact. This vicarious clearance probably accounts for some of the decrease in filtration fraction since it yields a level of apparent effective renal plasma flow which is greater than the volume of plasma perfusing functioning tubules.

The pattern of renal functional change in acute diffuse glomerulonephritis is seen as one which is widely variable, according to the severity of the lesion. In some patients most of the nephrons seem to be in active, if abnormal, function, while in others function is almost suppressed. The characteristic abnormality is a depression of glomerular filtration, measured either as a decrease in glomerular filtration rate, or more consistently, as a decrease in filtration fraction. With this is commonly associated an increase in the derived value RBF/TmD due to both hyperemia and to depression of TmD .

The decrease of filtration reflects the specific lesion of this disease, which is glomerular. The character of the renal change suggests that parts of the glomerular capillaries involved by the lesion become impermeable as filters, though their lumens may still be patent and permit the flow of blood. The presence of a predominantly glomerular lesion is confirmed in two of the patients by depression of the ratio GFR/TmD . The frequent decrease of TmD in this condition reflects loss of tubular secretory capacity due to one of

several causes. Among these, probably the most important is obstruction of glomerular capillaries with consequent suppression of excretory function in the nephrons. Another cause is obstruction of renal tubules by protein coagula (Oliver,²⁸ 1940; Blackman, Goodman and Buell,²⁹ 1941). It is also possible that the degenerative changes of tubule cells attributed to retention of protein reabsorbed from the protein-rich tubular fluid (Dock,³⁰ 1942) plays a part in inhibiting tubular secretion of diodrast. The increase in the function RBF/TmD is taken partly as a reflection of true renal hyperemia and partly as evidence of vicarious clearance of diodrast.

The Stage of Healing. Observations were made in four of the eight patients during the stage of healing. The pattern in two of the four patients is one of complete restoration to normal. In the other two patients the absolute level of function remains subnormal, although the derived values (FF , RBF/TmD) are normal, which suggests complete subsidence of an inflammatory reaction which, however, has been so severe that considerable portions of the kidneys are completely functionless.

Chronic Diffuse Glomerulonephritis (table 5b). Observations were made in 13 patients who were seen before they had reached the terminal phase of the disease (table 5c). As in the acute phase, the absolute levels of function are widely variable. It is somewhat surprising to find that both RBF and TmD were greater than mean normal in one patient and within the normal range in eight. Filtration fraction was reduced below normal in nine patients. The average level of this function is higher than in the acute phase. The ratio RBF/TmD is greater than mean normal in eight instances. The ratio GFR/TmD is decreased in seven of the patients. This change is taken as evidence of a predominantly glomerular defect. Hypoproteinemia is present in every instance. The renal functional pattern of one patient (no. 21) resembles that of malignant hypertension, as, at the time of observation, did the clinical syndrome.

Thus, the renal functional pattern in chronic diffuse glomerulonephritis is similar to that of the acute phase. It differs in that filtration fraction is more often within the limits of normal, in the uniform presence of hypoproteinemia, and in the appearance of a clinical and renal pattern similar to that of malignant hypertension in one patient. The parallelism of the functional pattern with that of acute glomerulonephritis indicates the similarity of structural changes present in the two phases of this disease. Depression of filtration reflects the glomerular lesion. Depression of TmD is due to the causes considered in discussing the acute phase. The increase in RBF/TmD in the chronic phase is probably wholly the result of vicarious clearance rather than of hyperemia. This is suggested (a) by the absence of absolute renal hyperemia in the chronic state of experimental glomerulonephritis and (b) the absence of structural evidences of hyperemia in sections from kidneys of patients suffering from chronic glomerulonephritis.

Terminal Chronic Glomerulonephritis (table 5c). The abnormalities of renal function present in this stage, their relation to the concurrent structural

changes and value in diagnosis and prognosis have been considered previously (Corcoran and Page³¹ (1944)). The outstanding features in this phase are (a) the extremely low levels of T_{mD} , (b) the comparatively low levels of RBF and GFR which are consistent with survival for periods of months and (c) the phenomenon of focal saturation.

The disproportionate reduction of T_{mD} as compared with other functions supports the view that the apparent renal hyperemia (increase in RBF/T_{mD}) observed in the chronic pre-terminal and acute phases of the disease are partly or wholly the result of vicarious clearance. A consequence of this severe loss of tubular secretory capacity is the appearance of focal saturation, i.e., of a state in which varying severity of the lesion in different nephrons results in some being saturated by the secretable substance (diodrast or p-amino-hippurate) at very low plasma concentrations while others are not. The presence of this is suggested by finding high levels of filtration fraction in a disease process in which it is probable that filtration is as much or more depressed than blood flow. The findings confirmed by titration of tubular secretion at varying plasma levels. The plasma clearance of diodrast obtained in this condition does not reflect effective renal plasma flow. Consequently the means of RBF, RPF and RR listed in table 6c do not include the six observations in which this phenomenon was present during the measurement of plasma clearance.

SUMMARY

Glomerulonephritis. The renal functional changes as observed in patients suffering from diffuse glomerulonephritis have been reviewed and the underlying mechanisms discussed by Earle, Taggart and Shannon²⁶ (1944). The patterns which they describe in the various phases of the disease are similar to those we present. The distortion of the pattern from the normal in the various stages of the disease are those which might be predicted from a knowledge of the concurrent structural changes, with the exception perhaps of the severe loss of tubular secretory capacity present in severe acute glomerulonephritis.

The differences in renal patterns between terminal glomerulonephritis and malignant hypertension with early renal failure have been reviewed previously, the most important points being the tendency in terminal glomerulonephritis to reduction of T_{mD} below 5 mg. per minute and of GFR below 10 c.c. per minute. In the other stages of the disease the differences between glomerulonephritis and hypertensive disease lie (1) in the presence in glomerulonephritis of a decrease in FF which persists at least until the disease is far advanced, (2) in the frequency with which the ratio RBF/T_{mD} is increased in glomerulonephritis, whereas it is decreased in the course of essential hypertension and (3) in the occurrence of a depression of the function GFR/T_{mD} in 9 of the 22 patients.

Since chronic glomerulonephritis at times causes a clinical syndrome indistinguishable from that of malignant hypertension, it is of interest that in

one such patient the renal functional pattern is that of malignant hypertension rather than that of the underlying but overshadowed glomerulonephritis.

(d) *Intercapillary Glomerulosclerosis.* Observations were made in six patients, four of whom were referred by Dr. E. P. McCullagh, suffering from intercapillary glomerulosclerosis (Kimmelstiehl-Wilson syndrome). These are listed in table 6a whence they may be compared with the pattern in glomerulonephritis.

The range of variation, like that of chronic glomerulonephritis, is very wide. The patterns are otherwise similar, with reduction in GFR, T_{mD} , FF, an increase of the ratio RBF/T_{mD} and in three patients a decrease of the ratio GFR/T_{mD} . As in chronic glomerulonephritis, there is no reason to ascribe the increase of the ratio RBF/T_{mD} to actual hyperemia of the residue of functioning tissue. Consequently, we attribute it to vicarious clearance. As in terminal glomerulonephritis, focal saturation and a very low level of T_{mD} are found in the terminal stage of the disease.

The mechanism of the change is similar to that of glomerulonephritis. The pattern is one of decreased filtration, presumably due to lesions of the glomerular capillaries which render many of them impermeable to filtrate, although still perfused by blood. With this is associated a loss of tubular secretory function due to actual loss of whole nephrons by (1) glomerular and (2) tubular occlusions and (3) to interference with the tubular functions of those which remain in partial function.

(e) *Toxemia of Pregnancy.* The renal functional pattern of the specific eclamptogenic toxemia of pregnancy is similar to that of acute glomerulonephritis (Corcoran and Page, 1941,³² 1942³³). The range of RBF varies from supernormal to subnormal levels. GFR and FF are depressed. T_{mD} tends to vary with the level of RBF. The pattern is one of interference with filtration. This has been attributed to constriction of afferent arterioles. We prefer to regard it as an expression of the glomerular lesion present in this condition (Bell,³⁴ 1945) in which increased renal interstitial pressure may also participate.

Delivery is followed by relief of toxemia and, in most cases, by complete restoration to normal of functional levels. A few post-toxemia patients show a persistent decrease of FF which is presumed to be a reflection of the persistent glomerular lesions found in post-toxemic women by Page and Cox³⁵ (1938). Others develop the clinical and renal functional manifestations of essential hypertension. In some of these the level of FF is frequently normal, i.e., less than would be predicted from clinical and renal functional state in a condition resembling established essential hypertension (Chesley,³⁶ 1941). This, like the low level of FF found in some post-toxemic normotensive women may reflect persisting healed glomerular damage. Since the renal and clinical functional pattern of essential hypertension may follow a toxemic pregnancy which was not preceded by hypertension, it seems likely that the hypertensive disease originates in the renal injury sustained during the toxemia.

The renal functional pattern of patients with essential hypertension persists unchanged during and after pregnancy except as it may be modified by the superimposition of specific toxemia of pregnancy. Observations similar to these have been made by Taylor, Wellen and Welsh³⁵ (1942), Chesley³⁰ (1941) and Dill, Isenhour, Cadden and Schaffer³⁷ (1942).

III. TOXIC NEPHROSIS

(a) *Vitamin D Intoxication.* In a previous report (Corcoran, Taylor and Page, 1943²⁷) we have discussed the course and probable interpretation of the renal functional changes occurring during toxic nephrosis due to inhalation of carbon tetrachloride. In this report we noted the similar patterns of injury in toxic nephrosis due to mercuric chloride and to oil of tansy. We therefore omit consideration of these conditions and shall only describe in this report the patterns found in renal injury due to vitamin D intoxication.

Observations were made in two patients during the course of an illness characterized by malaise, nausea and vomiting, evidences of renal impairment, metastatic vascular calcification and hypercalcemia which appeared during treatment with a product of the irradiation of ergosterol (Ertron). Clinical details of those and other similar cases form the substance of another report. The renal functional patterns in these two patients are shown in table 6b.

The pattern resembles that of other toxic nephroses. The predominance of tubular injury is indicated by the high ratios GFR/T_{mb} , which is the reverse of the change frequently found in acute and sub-terminal chronic glomerulonephritis. Withdrawal of the medication and symptomatic treatment has resulted in the recovery of these patients. The pattern during healing is shown for patient No. 41 seven months after the first observation. Evidence of healing in patient No. 40 consists in a urea clearance of 65 per cent of normal and a maximum urinary specific gravity of 1.024 eight months after the first observation.

(b) *Hemoglobinuric Nephrosis.* Experimental observations on the nature of the renal functional injury caused by administration of myoglobin and hemoglobin to dogs has been reported previously (Corcoran and Page,³⁹ 1945). These observations indicate that the renal lesion, which is not commonly severe, is partially due to obstruction of tubules by pigment deposits and partly to cytotoxic tubular changes. The latter are attributed to ingestion of the heme-pigments by the cells of the proximal tubules. The renal function most affected is T_{mb} .

SUMMARY

The renal functional pattern of toxic nephrosis is one of depression of all functions, principally of T_{mb} . Their nature demands great caution in interpretations of clearances determined in these states. Indeed, it has been shown that the interpretation usually attributed to plasma clearances of inulin

or diodrast are vitiated in such an experimental toxic nephrosis as that due to uranium nitrate (Bobey, Longley, Dicker, Price and Hayman,⁴⁰ 1943). The fallacy depends on loss of the selective permeability of renal tubules.

IV. FUNCTIONAL DISORDERS

The patterns of discrete renal functions are especially useful in characterizing renal disorders which are functional.

Thus, observations made during water deprivation, with consequent oliguria in young men (McCance, Young and Black,⁴¹ 1944) have shown that renal blood flow and glomerular filtration are normal. The only change is increased reabsorption of water. In clinical "dehydration" with loss of interstitial fluid and plasma volume, both renal blood flow and glomerular filtration are reversibly depressed.

Shock. The same changes occur in both experimental (Corcoran and Page,⁴² 1943a; Corcoran, Taylor, and Page,⁴³ 1943b; Phillips, Dole, Hamilton, Emerson, Archibald and Van Slyke,⁴⁴ 1945) and clinical (Lauson, Bradley and Cournand,⁵³ 1944) shock. The renal change which presages the onset of shock is a decrease of renal blood flow due to increased vascular resistance. A similar pattern is observed after severe gastrointestinal hemorrhage (Black, Powell and Smith,⁴⁶ 1941). The renal vasoconstriction is attributed by us largely to the action of a humoral vasoconstrictor entering the blood stream from injured tissues, other than liver or kidney. In severe shock the interpretation of the pattern is obscured, partly because of a redistribution of renal blood flow. This change may depend on shunting of blood from renal cortex to medulla, ascribed (Trueta, Barclay, Daniel, Franklin, and Pritchard,⁵¹ 1947) to vasomotor stimulation. But part of the abnormality of the pattern is probably dependent on altered permeability of tubules due to prolonged renal ischemia (Selkurt,⁴⁵ 1945).

These renal changes in shock are the basis of the severe renal failure of crush syndrome and related states, i.e., of the lower nephron nephrosis of Lucké⁴⁷ (1946). In most of these conditions renal failure is dependent on the superimposition of pigmentary precipitation on renal vasoconstrictive ischemia (Corcoran and Page,⁴⁸ 1947).

Arterial Hypotension. Because they illustrate the application of these procedures to functional disorders, we recapitulate observations made during hypotension due to ingestion of arsenic trioxide (Page, Taylor and Kohlstaedt) and idiopathic orthostatic hypotension (Corcoran, Browning and Page,⁴⁹ 1942).

The observations are summarized in table 6c. Minimal renal blood flow was maintained at a level of about two-thirds normal during severe hypotension due to arsenic. This rate of perfusion is sufficient to sustain normal tubular secretory activity, as is indicated by the level of TmD. While the level of arterial pressure (48 mm. Hg) found during the clearance test is usually insufficient to maintain glomerular filtration, the rate of filtration was measured at about one-third normal. The derived functions FF and GFR/

T_{MD} are also one-third normal. Calculation of resistances by the method of Lampport is impossible in this case, presumably because the greatly altered conditions changed the values allowed for yield pressure and tissue pressure in the equations. However, the maintenance of blood flow and filtration in the face of severe arterial hypotension testify to an extensive renal vasodilation. That peripheral vasodilation was present in a large vascular bed was confirmed by clinical examination and by the ballistocardiographic demonstration of a great increase in cardiac output.

These changes contrast with those found during orthostatic hypotension. In the patient under observation, this state appeared after an exhausting illness. The control levels of the renal functions were uniformly depressed. Tilting to 60° resulted in arterial hypotension. This was associated with decreases in RBF and GFR (T_{MD} was not measured but is assumed to be unchanged). FF was unchanged. Calculation of resistance indicates that the maintenance of FF is due to intraglomerular pressure having been sustained by efferent arteriolar constriction. Thus, the renal hemodynamic pattern in this hypotensive state contrasts markedly with the toxic vasodilation present in arsenic poisoning.

GENERAL SUMMARY

From observations in a wide variety of disorders which affect renal function, we summarize determinations of renal blood flow, glomerular filtration rate and tubular secretory capacity. The summaries consist in patterns of altered function which are shown to correspond with clinical, physiological and pathological estimates of the underlying renal changes, functional and structural.

The largest series of observations was made in patients suffering from hypertensive vascular diseases. The conclusions drawn are (a) that early essential hypertension is a functional disorder in which the only measurable renal abnormality is an increase of afferent resistance, presumably due to afferent arteriolar constriction, but that (b) as the process advances and evidences of extra-renal vascular damage appear, renal vasoconstriction becomes more intense, extends to both afferent and efferent arterioles, often results in renal ischemia and is associated with renal arteriolar sclerosis and resultant loss of secretory tissue. (c) In essence, the pattern in malignant hypertension is an exaggeration of these changes, characterized by rapid advance, but not, at its outset, associated with or caused by excretory insufficiency. By way of corollaries, we note that essential hypertension cannot be regarded as due to renal ischemia nor as a compensation for increased renal resistance due to vascular sclerosis and obliteration. (d) Arteriosclerotic hypertension is found to be associated with renal changes consistent with focal obliteration of afferent arterial channels.

In considering other diseases associated with arterial hypertension, attention is directed to the pattern in Cushing's syndrome, which is similar to

that of essential hypertension, but, in this small group, comparatively severe.

We note the diverse patterns in chronic pyelonephritis. When this condition is associated with arterial hypertension, the pattern is that of essential hypertension. Normotensive patients suffering from chronic pyelonephritis show a simple loss of function. Patients in whom the disease is active show patterns indicative of increased renal interstitial pressure, together with a severe loss of tubular function.

In diffuse glomerulonephritis, the renal pattern in the acute stage is shown to be one essentially of interference with glomerular filtration but with widely varying levels of blood flow and other functions which return towards normal during healing. The pattern in chronic glomerulonephritis is similar until the end stage when there is a very severe loss of tubular secretory tissue. The renal pattern in intercapillary glomerulosclerosis is shown to resemble that of chronic glomerulonephritis. That of specific toxemia of pregnancy is similar to that of acute glomerulonephritis.

In the toxic nephroses, the predominance of tubular injury is demonstrated in cases of vitamin D intoxication, and reference is made to findings in experimental hemoglobinuric nephrosis.

Finally, we contrast observations in orthostatic hypotension, in which there is little renal vasodilation, with those of hypotension due to arsenical intoxication, in which there is a severe renal vasodilation.

Thus, in a number of clinical disorders affecting renal function, the information yielded by the new tests of renal function is shown to indicate the nature of the changes occurring in the kidney. The estimates obtained from such studies are more precise, as regards circulatory and excretory aspects of renal function, than any which can be derived in the functional assay of other organs by present methods.

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CLINICAL APPRAISAL OF BENADRYL, PYRIBENZAMINE, AND ANTHALLAN IN THE TREATMENT OF ALLERGIC DISORDERS*

By MARTIN S. KLECKNER, JR., Captain, Medical Corps, A.U.S.,†
Allentown, Pennsylvania

DURING the past year there have been numerous reports of remarkable advances in the treatment of various types of allergic reactions through the use of three drugs in particular which appear to have the action of neutralizing the effects of histamine. I refer to the new "antihistamine" preparations that have become available: Benadryl, Pyribenzamine, and Anthallan. The therapeutic usefulness of these pharmaceuticals has led to widespread acclaim by the laity, to hundreds of back orders in drug stores, and to exaggerated propaganda by the press and radio. This was particularly true during the dreaded hay-fever season when untold numbers of sufferers were told of the new "allergic panacea" of medical science. Internists in particular feared that indiscriminate use of the drugs might outweigh whatever beneficial effects they might possess.

For the most part, it is assumed that the liberation of histamine in sufficient concentration accounts for the signs and symptoms of anaphylaxis and allergic reactions.¹ Histamine is known to produce contraction of smooth muscle, especially in the bronchioles, blood vessels, intestines, and uterus; to cause dilatation and increased permeability of the capillaries of the skin and mucous membranes; to act as a secretagogue in the glands of exocrine secretion such as the salivary, gastric, intestinal, pancreatic, and the respiratory tract glands; and lastly to induce pain at the site of injection in the skin.² It is reported that histamine appears in the blood immediately after the administration of an antigen, and that in the guinea pig the phenomena of anaphylaxis and those following the administration of histamine are identical.³

The production of an allergic state results from the linkage of certain fixed cells or antibodies with a specific antigen, from which union there results a liberation of histamine. It has been stressed in the past that allergy is not a single or uniform biologic phenomenon. There are different varieties of anaphylaxes varying from an induced physiological allergy, such as serum sickness or bacterial sensitivity, to a spontaneous, pathologic or hereditary allergy exemplified by hay-fever or angioneurotic edema.⁴ The etiologic agents concerned in allergic reactions are well known.

Although it has generally been considered that a trial with an antihistamine substance would lead to interesting results in the treatment of allergic manifestations, it was not until recently that Loew, Kaiser, and

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† The author is a fellow-elect in Internal Medicine at the Mayo Foundation, Rochester, Minnesota.

Moore^{5,6} discovered that, of all the synthetic benzhydryl alkamine ethers used in alleviating anaphylaxis and histamine shock in experimental animals, betadimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) was the most effective studied. It appeared to be more effective than theophylline-ethylene diamine (Aminophylline) in relieving bronchial constriction and diminishing the depressor effects of histamine and acetylcholine while alleviating the vasopressor effects of histamine and smooth muscle spasm. McElin and Horton⁷ of the Mayo Clinic report convincing experimental evidence demonstrating the ability of Benadryl to combat certain actions of histamine such as vasodilatation, histamine-induced nasal congestion, and rise in gastric acidity. They review a small series of allergic cases, in which both oral and parenteral Benadryl were administered. The latter technic was used in experimental cases, and excellent results were obtained in a large majority of instances. They discovered that sleepiness, dizziness, dry mouth, nervousness, and urinary frequency were the predominant side effects of the drug.

O'Leary and Farber⁸ found that Benadryl was extremely effective in the treatment of urticaria and angioneurotic edema. They found the drug only palliative in effect, though it produced complete relief in 34 of a series of 50 patients and definite improvement in 12. The use of Benadryl in hay-fever and bronchial asthma has been thoroughly studied. One group found it benefited 75 per cent of hay-fever patients, 74 per cent of patients having concomitant hay-fever and asthma, and 33 per cent of cases of bronchial asthma.⁹ Williams found Benadryl to be effective in treating physical allergy of the head, especially vasomotor rhinitis.¹⁰ Logan has employed Benadryl successfully in the treatment of allergic conditions of childhood.¹¹ In a very early report on the use of this drug Curtis and Owens¹² administered Benadryl to 18 patients who had acute and chronic urticaria and noted immediate relief of signs and symptoms in 11, definite improvement in three, and no benefit whatsoever in four. In an excellent article Code¹ reviews the pharmacology of Benadryl and its action as an antihistamine substance. He implies that there is still much to be understood in histamine metabolism and in the interpretation of the action of Benadryl before one comes to definite conclusions regarding its properties. Friedlander and Feinberg¹³ have stated that Benadryl given orally causes slight inhibition of histamine wheal, whereas a marked reduction follows its local application. It is interesting to note that these investigators actually found Benadryl, in a single oral dose of 100 mg., to cause a slight reduction in both systolic and diastolic blood pressures for several hours. They remark that this phenomenon was central in origin as is the side effect of drowsiness. Thacker,¹⁴ in a very well organized survey, found Benadryl to offer 30 per cent complete relief, 20 per cent definite improvement, and 50 per cent slight or no benefit in the treatment of vasomotor rhinitis; and 28.5 per cent complete relief, 14.3 per cent definite improvement, and 57.1 per cent slight or no benefit in the treatment of perennial allergic rhinitis. Only half of his patients with allergic rhinitis

and bronchial asthma manifested definite improvement. This series, however, was unfortunately small in number.

Waldbott,¹⁵ in treating 165 cases of urticaria with Benadryl, found complete relief in 80 per cent of cases treated. In this series relief was afforded within four hours after oral administration of one capsule. He found Benadryl to effect complete relief in 32 per cent and partial relief in 18 per cent of cases with perennial bronchial asthma; 30 per cent and 16 per cent in seasonal bronchial asthma; 51 per cent and 23 per cent in hay-fever; and 43 per cent and 31 per cent in vasomotor rhinitis. On the bases of this experience he considered the effect of the drug to be more pronounced on the allergic wheal than on bronchospasm. Eyermann¹⁶ gave Benadryl to a series of 52 patients with vasomotor rhinitis and found that 67 per cent experienced complete relief, and that sneezing was abated in the remaining 23 per cent. One report deals with the successful treatment of an insulin allergy with Benadryl.¹⁷ O'Leary and Farber¹⁸ have successfully treated urticaria, scleroderma, and allied dermatoses with large doses of oral Benadryl but caution against the indiscriminate use of the drug because of the severe side reactions. Feinberg¹⁹ insinuates that Benadryl gives no lasting benefit but only palliative effect; he likewise stresses limitations of the drug because of the undesirable side reactions. Sixty per cent of Levin's series manifested the side effect of drowsiness, and the withdrawal of the drug led to symptomatic relapse.²⁰ Schwartz and Levin²¹ have used Benadryl with reasonable success in a small series of allergic disorders. Numerous other reports concerning the therapeutic value of Benadryl are available, though the efficacy of this drug in the treatment of dysmenorrhea, migraine, and various cutaneous disorders is questionable.

Mayer²² lists two main groups of substances exhibiting antihistamine properties: (1) amino acids such as arginine, histidine, and cysteine, and (2) certain aromatic derivatives of amino-ethanol and ethylene-diamine. He advances a hypothesis that these antihistamine substances compete with histamine to displace it from the site of action, similarly to the action of para-amino-benzoic acid in the displacement of the sulfonamide drugs. He believes that the action of the anti-histamine substances is upon what, according to the theory of histamine effect, is the last phase of the allergic or anaphylactic reaction. Feinberg,²³ in a recent report concerning the experimental and therapeutic status of histamine and antihistamine drugs, mentions the relative merits of the recent French antihistamine agents, namely the Fourneau and Mosnier compounds, and concludes that their toxicity is too great to warrant their therapeutic use. His article is a brilliant, comprehensive review of the recent pharmacological aspects of allergy control.

Ciba Pharmaceutical Products, Inc., have introduced Pyribenzamine Hydrochloride, chemically N'-pyridyl-N'-benzyl-N-dimethyl ethylene diamine hydrochloride. This product, like Benadryl, is a white crystalline substance, is stable, and is readily soluble in water; it has been shown to counteract histamine intestinal spasm, histamine asthma, histamine shock, anaphylactic

shock, and to abolish histamine skin wheals in experimental animals. Whereas Benadryl is supplied in both 25 mg. and 50 mg. capsules and in an elixir vehicle by the Parke, Davis & Company, Pyribenzamine at present is dispensed in 50 mg. tablet form.²⁴ Arbesman, Koepf, and Miller²⁵ found Pyribenzamine to have variable antianaphylactic activity, though exhibiting no demonstrable effect on the precipitin or complement titer in guinea pigs. When this drug was administered orally 18 out of 28 subjects presented decreased histamine wheals. These investigators disclosed diminished skin reactivity in 14 out of 24 allergic patients, and also a reduced reactivity of the skin sites which were passively sensitized with serum containing cottonseed reagins. They found improvement with Pyribenzamine in 95 per cent of cases of acute urticaria, 70 per cent of cases of chronic urticaria, 85 per cent of cases of seasonal hay-fever, 73 per cent of cases of extrinsic rhinitis, 50 per cent of cases of intrinsic rhinitis, 50 per cent of cases of seasonal bronchial asthma, 49 per cent of cases of extrinsic non-seasonal bronchial asthma, and 25 per cent of cases of intrinsic non-seasonal bronchial asthma. Epstein²⁶ found Pyribenzamine to afford excellent relief in the treatment of acute and chronic urticaria and atopic dermatitis. Osborne, Jordan, and Rausch²⁷ list Pyribenzamine as a successful agent in the treatment of certain allergic disorders including chronic atopic dermatitis, physical allergy, and dermatitis herpetiformis. The predominant side effects reported were of less severity than those observed with the use of Benadryl. Minor side reactions have been reported in 30 per cent of cases, the most frequent of which were drowsiness, nausea, headache, dizziness, dryness of the mouth, nervousness, and abdominal discomfort, in the order given. The recommended dosage has been the same as Benadryl, 50 mg., but because of individual variation as little as 50 mg. and as high as 600 mg. have been used.²⁴ For most patients 50 mg. twice to four times daily after meals usually suffices.

The third product just recently made available to the medical profession for the treatment of allergic rhinitis and allergic skin manifestations is Anthallan, a synthetic organic substance with chemical formula of 3'-di(n-butyl)amino-methyl-4,5,6-trihydroxy-benzo-(1,2-c)furan-1'(3')-one, $C_{17}H_{23}O_5H$; it is a lactone of beta-gallic acid-ethanol-alpha-di(n-butyl)amine. The mild antihistamine action of Anthallan is based on the fact that it antagonizes lethal doses of histamine in guinea pigs, causes abolition or suppression of histamine-induced spasms in guinea pig uterus or intestine, diminishes the vasoconstrictor action of histamine, manifests rebound blood pressure rise after primary histamine lowering of blood pressure, and suppresses anaphylactic shock in sensitized guinea pigs. This drug is relatively non-toxic, and no intolerance to it has been observed in experimental animals.²⁸ Ghiselin²⁹ has reported a series of 48 seasonal and non-seasonal allergic rhinitis cases in which Anthallan was administered. In an elaborate method of grading the degree of improvement registered by each patient, this report discloses that benefit from Anthallan was found in 90 per cent of patients studied, the improvement varying between 25 and 100 per cent objectively and sub-

jectively. The controlling factor in this experiment has been questioned, and the newly coined term, "hyperesthetic rhinitis," has met with some disapproval.³⁰ Results in the Gliselin trials were obtained over a period of seven to 35 days in patients selected on the basis of certain diagnostic criteria. Frequently the degree of improvement could be noticed within the first week. No significant variation in laboratory findings was observed, and the only side reactions noticed were one case of diarrhea and one of acute dermatitis. Schwartzschild³¹ used Anthallan to treat 35 cases of neurodermatitis disseminata, 41 cases of urticaria, and eight cases of papular urticaria, all of which were resistant to or unimproved by other types of therapy. In this significant series benefit was found in 80 per cent of cases, the improvement varying between 50 to 100 per cent by scale. One case developed an attack of diarrhea which subsided upon discontinuation of Anthallan. A complete and persistent subsidence of infantile eczema in twins after three weeks of treatment employing Anthallan is reported.²⁸ Ereaux and Craig³² have used Anthallan successfully in treating infantile eczema and atopic dermatitis. Particularly large doses were used in this series of cases.

Anthallan is supplied in individual capsules containing 85 mg. of the drug, the recommended oral dosage being two capsules after each meal. A three weeks' course of therapy is suggested, and in a surprising number of cases, particularly infantile eczema and atopic dermatitis, permanent cure results. Though this drug possesses mild antihistamine properties, its mode of action still remains obscure. Many unsuccessful courses of treatment have been the result of inadequate dosage, and initial large doses of Anthallan are advised until a smaller maintenance dose can be managed after several weeks. It is important that all infectious cases be eliminated before Anthallan is administered so as to assure consistent results. The research division of the Medico Chemical Corporation of America, manufacturers of Anthallan, has reported several cures of allergic skin disorders within recent months.²⁸

CLINICAL STUDIES

The purpose of these studies was to test the efficacy of Benadryl, Pyribenzamine, and Anthallan in the treatment of various common allergic disorders. The author feels that the current widespread indiscriminate use of these products without proper attention to a thorough allergic examination constitutes a definite danger. The work here reported was carried out at the Umatilla Ordnance Depot, Ordnance, Oregon, where the author was Post Surgeon at an active station hospital. Here the situation was particularly favorable for observing cases of hay-fever, asthma, and various perennial allergic manifestations, as the depot is located on a large plateau of sand and desert weeds, and, because of the continuous activity of the wind, pollens, dust, and animal emanations are widely disseminated throughout the countryside. All allergic cases were studied completely. The following routine examinations were carried out in order effectively to standardize the series:

physical examination, routine laboratory studies, nasal smears including determination of eosinophilia, sinus and chest roentgenograms when indicated, cutaneous skin tests for specific allergens in many cases, and a complete otorhinolaryngological examination. For the most part the patients had never been desensitized and were not taking concomitant therapy at the time of the experiment except vasoconstrictor nose-drops or patented ephedrine-phenobarbital tablets in a few cases. An extensive history was taken in an attempt to discover seasonal variation, familio-hereditary traits, and the type and onset of discomfort. The patients were either military personnel, laborers at the depot, or civilians living in the area. Excellent coöperation by all patients was obtained throughout the trial test, and none had the opportunity of altering his environment. Every patient had the procedure completely explained to him and was instructed to eliminate any extraneous factors, such as noxious fumes, irritating gases, paints, etc., that would interfere with the end results of the experiment. Often throughout the course placebos were administered in a manner which effectively concealed their identity. For example, when drowsiness became an outstanding side reaction, 60 mg. of phenobarbital was given orally and the consequences noted. As the terminology "vasomotor rhinitis" is often misinterpreted, the following diagnostic criteria (Thacker³³) were used: (1) intermittent nasal congestion, alternating or bilateral, for one year or more; (2) normal appearance of the mucosa of the turbinates, which, if slightly hyperemic, demonstrated little or no excess nasal secretion; (3) enlarged turbinates which shrank well with vasoconstrictor medicaments; (4) negative history for allergy, negative nasal smears for eosinophiles, and cutaneous tests which revealed no sensitivity.¹⁴ In addition to the above criteria, cases were selected for study that were relatively free of emotional disturbance or nervous tension which might interfere with their existing disorder. For each drug the minimal length of the test period was 21 days, the average time being 30 days. Using the aforementioned criteria 170 cases were selected from available clinical material, eight of which were subsequently used for control purposes. In many cases, after results were assured with a particular drug, a short period of time would be allowed to elapse before trial of another drug. In a small series of cases successive trials of the three drugs were successfully accomplished. Patients were interviewed and examined twice a week to determine the degree of palliation afforded by the drug and the occurrence of side effects.

The clinical results in 106 cases of allergic disorders treated with oral Benadryl are tabulated in table 1. By comparing the figures, it may be stated that there is evidence that Benadryl alleviates the histamine wheal more effectively than it abolishes bronchospasm. Benadryl produced effective palliation in seasonal allergic rhinitis (grasses-ragweed), angio-neurotic edema of the skin, and acute urticaria, but was less beneficial in perennial allergic rhinitis, vasomotor rhinitis, and seasonal allergic rhinitis with bronchial asthma. It was least effective in seasonal bronchial asthma. Although sufficient relief was afforded patients with atopic dermatitis, the

small number of cases studied introduces a wide margin of error. Although the average dosage of Benadryl used was 100 mg. daily, it was found necessary to raise the dosage to 150 mg. in cases of seasonal allergic rhinitis with bronchial asthma, vasomotor rhinitis, and angioneurotic edema. Urticaria and angioneurotic edema disappeared completely within four to six hours, whereas 48 to 72 hours were required for the cutaneous remission of atopic dermatitis. Continuous therapy was necessary to avoid relapses in the latter condition. Seasonal bronchial asthma necessitated the administration of an average of 50 mg. four times a day, and patients were often compelled to increase this amount to 300 mg. daily. It is interesting to note that in 8 per cent of the cases complete failures occurred in treating seasonal bronchial asthma with Benadryl, whereas no failures were encountered in treating the other allergic disorders. Most patients found that taking 50 to 100

TABLE I
Clinical Results with Benadryl

Predominant Allergic Manifestations	No. of Cases	Aver. Yrs. Symptom	Aver. Daily Dosage	Aver. Yrs. Age	Degree Relief Afforded			
					Great	Mod.	Slight	None
1. Seasonal Allergic Rhinitis (Grasses-Ragweed)	39	11	100 mg.	34	31 (80%)	6 (15%)	2 (5%)	0
2. Vasomotor Rhinitis	10	14	150 mg.	27	6 (60%)	3 (30%)	1 (10%)	0
3. Perennial Allergic Rhinitis (Extrinsic-Intrinsic)	21	10	100 mg.	28	15 (71%)	4 (19%)	3 (10%)	0
4. Seasonal Allergic Rhinitis with Bronchial Asthma	22	12	150 mg.	32	14 (64%)	6 (27%)	2 (9%)	0
5. Seasonal Bronchial Asthma	12	12	200 mg.	26	6 (50%)	3 (25%)	2 (17%)	1 (8%)
6. Angioneurotic Edema (Skin)	4	3	150 mg.	24	4 (100%)	0	0	0
7. Acute Urticaria	6	5	100 mg.	27	5 (83%)	1 (17%)	0	0
8. Atopic Dermatitis	2	4	100 mg.	34	1 (50%)	1 (50%)	0	0

mg. of Benadryl prior to sleep aided remarkably in combating nocturnal asthma. For the most part patients expressed the opinion that palliation of symptoms occurred generally within one hour after ingestion of the drug, the effects lasting three to four hours. It was found that Benadryl could prevent asthmatic attacks, but the oral route was ineffective in aborting a sudden attack. As this series deals only with Benadryl, mention will be made in later pages concerning the wisdom of concomitant therapy. Although not the immediate subject of this study it is worthwhile to note that Benadryl in average doses was found effective in treating drug idiosyncrasies such as barbiturate or iodide cutaneous reactions, serum sickness and urticaria from tetanus antitoxin, acute urticaria and bullous dermatitis from penicillin sensitization, and food allergy. Moderate to slight relief was afforded patients with allergic bronchitis, severe intrinsic bronchial asthma, migraine, and Ménière's disease.

One hundred and 11 cases of allergic disorders were treated with Pyribenzamine, and here again it was noticed that the histamine wheal was more effectively abolished than bronchospasm. Thus, in hay-fever, perennial allergic rhinitis, acute urticaria, and atopic dermatitis, outstanding palliative results were obtained, but seasonal allergic rhinitis in combination with bronchial asthma and uncomplicated bronchial asthma were afforded less relief. It is interesting to note that 7 per cent of the failures were found in seasonal allergic rhinitis (grasses-ragweed). Fifty per cent of cases of vasomotor rhinitis experienced complete relief, and another 25 per cent experienced moderate to slight relief from Pyribenzamine therapy. Whereas a greater number of complete failures were observed with Pyribenzamine than with Benadryl in alleviating the distressing symptoms of seasonal bronchial asthma, there was a greater incidence of moderate and slight relief noted. The average dosage of Pyribenzamine was 200 mg. daily divided into four equal doses. The alleviation of rhinorrhea and conjunctival irritation in seasonal allergic rhinitis could be accomplished with 150 mg. of Pyribenzamine. There was little variation in the degree of relief afforded patients suffering from seasonal allergic rhinitis with bronchial asthma by administering 300 mg. instead of the recommended 200 mg. It was necessary for the most part to treat bronchial asthmatics with 300 mg. of Pyribenzamine daily, and often another 50 to 100 mg. was used prior to bedtime to abate any nocturnal asthma. Although 100 per cent of cases of atopic dermatitis experienced great relief with Pyribenzamine within several days, obviously the number of cases is too small to make any generalization. Continuous therapy was necessary to avoid relapses. Patients noted palliation of symptoms from Pyribenzamine within 45 minutes to an hour following administration, and the length of relief was usually three to four hours. Similarly,

TABLE II
Clinical Results with Pyribenzamine *

Predominant Allergic Manifestations	No. of Cases	Aver. Yrs. Symptoms	Aver. Daily Dosage	Aver. Yrs. Age	Degree Relief Afforded			
					Great	Mod.	Slight	None
1. Seasonal Allergic Rhinitis (Grasses-Ragweed)	42	12	150 mg.	32	30 (72%)	6 (14%)	3 (7%)	3 (7%)
2. Vasomotor Rhinitis	8	13	200 mg.	36	4 (50%)	2 (25%)	2 (25%)	0
3. Perennial Allergic Rhinitis (Extrinsic-Intrinsic)	20	11	200 mg.	28	16 (80%)	3 (15%)	1 (5%)	0
4. Seasonal Allergic Rhinitis with Bronchial Asthma	22	10	200 mg.	30	8 (36%)	10 (46%)	4 (18%)	0
5. Seasonal Bronchial Asthma	21	14	300 mg.	38	1 (8%)	3 (25%)	6 (50%)	2 (17%)
6. Acute Urticaria	5	5	200 mg.	27	4 (80%)	1 (20%)	0	0
7. Atopic Dermatitis	2	4	200 mg.	34	2 (100%)	0	0	0

* Pyribenzamine Hydrochloride was generously supplied by the Ciba Pharmaceutical Products Inc., Summit, N. J.

Pyribenzamine was noted to act better as a prophylactic agent against bronchial asthma than in treatment of an asthmatic attack.

The third drug that was clinically tested on allergic disorders was Anthallan, but because of the limited amount available at the time of the experiment a considerably smaller number of cases was studied. In comparison with the other antihistamine drugs, this substance is, on the whole, untested in clinical cases; therefore, every attempt was made to keep the experiment rigidly controlled, and meticulous care was exercised to eliminate any extraneous factors that would alter the results in this small series of cases. Anthallan was found to exhibit very weak antihistamine properties, having practically no antibronchospastic qualities. This is in agreement with the findings of other investigators.²⁸ The dosage used was two 85 mg. capsules three times a day. This was the minimum dose, and most often it was raised whenever inadequate results were secured. For the first two to three weeks this routine was maintained, and, in most subjects with the exception of bronchial asthmatics, it was soon found that a maintenance dose of one capsule three times daily could eventually be employed. Cases of seasonal allergic rhinitis, perennial allergic rhinitis, acute urticaria, and atopic dermatitis responded quite effectively to Anthallan. I feel that any failures occurring with this drug, excluding bronchial asthma cases, could probably be minimized if larger doses over a longer period of time were used. The failure in 17 per cent of vasomotor rhinitis cases is significant, and the complete failure of Anthallan to prevent asthmatic attacks again indicates its apparent weak antihistamine character. Half of the patients treated with Anthallan had previously been tried with Benadryl or Pyribenzamine for a period of not over three weeks during the height of the seasonal pollination, a rest period from three to five days being permitted before clinical comparison with Anthallan. This procedure was followed to minimize the clinical error. Although satisfactory results were obtained in relieving cases of urticaria and atopic dermatitis, the number of cases again is too small for any general conclusions to be drawn. However, my experience with Anthallan, since the time of the study, in regard to acute and chronic urticaria, angioneurotic edema, atopic dermatitis, and two cases of drug idiosyncrasy leads me to believe that Anthallan is invaluable in the treatment of these disorders, particularly since no toxic reactions from the drug have been personally witnessed.

It was noted that the major disadvantage with both Benadryl and Pyribenzamine is the large number of undesirable and uncomfortable side reactions that were prevalent. In this investigation Benadryl was found to give almost twice the number of side reactions as Pyribenzamine. In the former series, 72 per cent of the cases exhibited them as against 43 per cent for the Pyribenzamine series. In agreement with other investigators, it was discovered that somnolence, fatigability, dry mouth, dizziness, urinary frequency, feeling of nervousness, and epigastric distress were the predominant side effects for both drugs with the possible exception of dizziness which was

found in only 2 per cent of the Pyribenzamine series. Other less common side reactions are listed in table 4, and it is noted that tinnitus, shortness of breath, pallor, blurred vision, and palpitation were encountered only with Benadryl. Two cases treated with Benadryl and one case with Pyribenzamine were forced to discontinue treatment because of exhaustion; in addition one case of narcolepsy was observed with Benadryl. Peculiarly enough it was found that children were more immune to side reactions from both Benadryl and Pyribenzamine than adults, the dosage having no bearing on the case. In a great many cases tolerance to side reactions would develop after several days of therapy. Often the administration of caffeine tablets, a cup of strong tea or coffee, or 10 mg. of amphetamine sulfate (Benzedrine) was used to combat drowsiness, and in particular fatigue. Though the ana-

TABLE III
Clinical Results with Anthallan *

Predominant Allergic Manifestations	No. of Cases	Aver. Yrs. Symptoms	Aver. Daily Dosage	Aver. Yrs. Age	Degree Relief Afforded			
					Great	Mod.	Slight	None
1. Seasonal Allergic Rhinitis (Grasses-Ragweed)	22	11	.51 gm.	34	14 (64%)	4 (18%)	2 (9%)	2 (9%)
2. Vasomotor Rhinitis	6	14	.51 gm.	26	1 (17%)	1 (17%)	3 (50%)	1 (17%)
3. Seasonal Allergic Rhinitis with Bronchial Asthma	18	10	.51 gm.	32	4 (22%)	5 (28%)	4 (22%)	5 (28%)
4. Perennial Allergic Rhinitis (Extrinsic-Intrinsic)	12	8	.51 gm.	22	9 (75%)	2 (17%)	1 (8%)	0
5. Seasonal Bronchial Asthma	10	12	.51 gm.	38	0	1 (10%)	5 (50%)	4 (40%)
6. Acute Urticaria	2	2	.51 gm.	34	2 (100%)	0	0	0
7. Atopic Dermatitis	3	4	.51 gm.	27	2 (67%)	1 (33%)	0	0

* Anthallan was generously supplied by the Medico Chemical Corporation of America, New York, N. Y.

leptic and sympathomimetic properties of the latter drug were realized, in no case was there noted any exacerbation of the underlying allergic disorder. Particularly in employing Benadryl, it was noted in some cases that side reactions were definitely the result of overdosage, and proper adjustment was effectively made. Somnolence, fatigability, dizziness, and nervousness in particular can endanger the patient's welfare during the course of his daily routine. Benadryl was found to be the contributing cause to an industrial accident.³⁴ Shocklike reaction,³⁵ epileptiform seizure,³⁶ prolonged reaction,³⁷ and the danger of self medication and large dosage³⁸ are but a few recently reported severe dangers from Benadryl therapy. For this reason the administration of Benadryl should always be under a physician's guidance.

In the series treated with Anthallan there was no evidence of side reactions. This made utilization of the drug exceedingly advantageous. Perhaps this is explained by the low antihistamine property of the drug. One

case of nausea from Anthallan was cured when the capsules were administered following meals according to the general directions for use of the drug.

The use of Benadryl, Pyribenzamine, and Anthallan is a valuable contribution in symptomatic control over several allergic disorders, but these drugs are not a substitute for a complete history and physical examination, adequate laboratory procedures, allergic skin tests, and roentgenograms of the sinuses and chest or anything conducive to a complete allergic study of the patient. The neglect of such basic procedures is apt to become the most serious disadvantage resulting from the introduction of the antihistamine drugs. These drugs are no substitute for desensitization to an offending allergen or a change from a particularly unfavorable environment. They may be considered as only a valuable adjunct to any allergic régime. Often concomitant therapy should be considered. The use of vasoconstrictor nose drops as a temporary relief from nasal congestion may be considered, but the patient must be warned that overuse of these is a dangerous procedure. Rhinitis medicamentosa is a severe consequence that is commonly encountered in the treatment of chronic nasal obstruction.³⁹ The use of expectorants particularly in allergic bronchitis and bronchial asthma as concurrent therapy with the antihistamine drugs was found very effective. In this respect

TABLE IV
Comparative Incidence of Side Reactions

Side Reactions	Benadryl (Average Dosage 100 mg. daily; 96 cases)	Pyribenzamine (Average Dosage 200 mg. daily; 91 cases)
1. Somnolence	62 cases (65%)	24 cases (26%)
2. Fatigability	54 cases (56%)	12 cases (13%)
3. Dry Mouth	52 cases (54%)	22 cases (24%)
4. Dizziness	29 cases (30%)	2 cases (2%)
5. Urinary Frequency	14 cases (15%)	13 cases (14%)
6. Nervousness	12 cases (13%)	12 cases (13%)
7. Epigastric Discomfort	6 cases (6%)	4 cases (4%)
8. Headache	3 cases (3%)	4 cases (4%)
9. Bad Taste	3 cases (3%)	4 cases (4%)
10. Nausea	3 cases (3%)	1 case (1%)
11. Tinnitus	2 cases (2%)	0
12. Discontinuation of Drug	3 cases (3%)	1 case (1%)
13. Shortness of Breath	1 case (1%)	0
14. Pallor	1 case (1%)	0
15. Exhaustion	1 case (1%)	1 case (1%)
16. Blurred Vision	1 case (1%)	0
17. Palpitation	1 case (1%)	0
18. Hot Flashes	1 case (1%)	1 case (1%)
19. Coldness of Extremities	1 case (1%)	1 case (1%)
20. Confusion	1 case (1%)	0
21. No Side Reactions	27 cases (28%)	52 cases (57%)

potassium iodide, ammonium chloride, or elixir of terpin hydrate were utilized. Aminophylline in doses of 0.2 gm. orally may act synergistically in relieving bronchospasm; nadin may be employed with reasonable success. The use of hapamine with the antihistamine drugs is as yet untried. Non-specific desensitization with histamine diphosphate has been disappointing in treating allergic disorders, although it has cured migraine and histamine cephalalgia successfully. It has been my experience that a low sodium, high

potassium régime produces minimal effect, if any at all, in relieving allergic trouble. Thacker,³³ in a complete survey of chronic nasal obstruction, has recommended highly the injection of the turbinates with sclerosing solutions, if less radical measures fail to afford proper relief. The indiscriminate use of vasoconstrictor-sulfonamide, tyrothricin, or penicillin nose drops should be avoided because of the possible development of bacterial fastness. Investigation of the functional or psychiatric factor in allergic diseases is of paramount importance, and control of this can be considered as valuable as relief of organic distress. Lastly, a proper, well-balanced diet, adequate rest, and good hygiene is most desirable. These are some of the palliative measures that may be effectively used in conjunction with the new antihistamine drugs.

The advent of Benadryl, Pyribenzamine, and Anthallan is a major step in conquering the distressing symptoms of hay-fever and other allergic reactions. They are by no means a panacea and offer only palliative effects, but they are the first antihistamine drugs that have met with reasonable success in treating a wide variety of allergic disorders. The accompanying tables demonstrate their comparative effectiveness and toxicity. An allergic patient, following complete study, may be tried on one or another of the drugs to determine their efficacy and the minimum of undesirable side reactions. Our observations indicate that Benadryl is the most potent antihistamine compound in relieving clinical bronchospasm, but it causes uncomfortable and often serious side effects in over 50 per cent of patients. Pyribenzamine, on the other hand, can compare favorably with Benadryl in most allergic disorders except asthma and causes less distressing and only half as many side reactions. Anthallan was found to possess very weak antihistamine properties, if any at all, but was very valuable particularly in treating skin disorders having an allergic background. Its relative freedom from side effects is a major advantage. Seasonal and non-seasonal allergic rhinitis and vasomotor rhinitis could be handled effectively with either Benadryl or Pyribenzamine, the latter offering more cures.

Bronchial asthma was the allergic disorder most resistant to all three drugs. Benadryl was found to be the most efficacious of the three in this condition but gave partial relief in only 25 to 50 per cent of patients. Anthallan offered considerable relief to hay-fever patients in particular but had a higher percentage of failures than the other drugs. Atopic dermatitis, acute and chronic urticaria, and angioneurotic edema may be considered to be effectively treated with the three drugs, but a larger series of patients is preferred for final judgment. Peculiarly enough, using Anthallan in large doses over a long period of time caused an apparent cure in the allergic skin disorders inasmuch as no relapses were noted in the patients studied. Vasomotor rhinitis was treated with reasonable success with the three drugs. It may be advisable to give each drug a trial test in this condition.

In a good number of cases it was considered that the ideal treatment of the allergic disorder was perennial desensitization with the allergen, together

with concurrent use of the antihistamine drugs. At present, however, their value still appears to be the temporary relief of various allergic symptoms. If infection plays a leading part in the disorder, eradication of the infective focus is considered mandatory. On the whole, it is too early to give a complete estimate of Benadryl, Pyribenzamine, and Anthallan in counteracting allergic symptoms. Their long-range effectiveness, tolerance, and clinical limits are still unanswered questions. Final judgment must be reserved until future studies are completed.

CONCLUSIONS

1. Benadryl, Pyribenzamine, and Anthallan are effective agents in treating many allergic disorders, presumably by neutralizing the effects of histamine.

2. The drugs are not a panacea and offer only palliative treatment. Anthallan, however, in a great many cases has produced an apparently permanent cure.

3. Benadryl has been found to be the most potent drug of the series in the treatment of seasonal and perennial allergic rhinitis, vasomotor rhinitis, bronchial asthma, urticaria, angioneurotic edema, and atopic dermatitis. It causes, however, a large number of undesirable side reactions which may endanger the welfare of the patient.

4. Pyribenzamine has been found effective in treating the above allergic disorders, though possessing less potency than Benadryl. It possesses a chief advantage of causing only half as many side reactions as Benadryl.

5. Anthallan is a weak antihistamine agent and has been found effective in treating allergic rhinitis and vasomotor rhinitis. Its outstanding quality appears to be the prevention of relapses in acute and chronic urticaria, angioneurotic edema, atopic dermatitis, and infantile eczema. No toxic side effect was encountered.

6. In accordance with other investigators this study reveals somnolence, fatigability, dry mouth, dizziness, urinary frequency, nervousness, and epigastric discomfort as the chief side reactions of Benadryl and Pyribenzamine.

7. There is no substitute for an adequate investigation into the allergic problem, and the antihistamine drugs should not be used until the exact nature of the problem is ascertained.

8. Concomitant therapy may be effectively administered.

9. Indiscriminate use of Benadryl, Pyribenzamine, and Anthallan should be discouraged because of the severe side reactions encountered, particularly with Benadryl and Pyribenzamine.

10. Future studies must be carried out before the definitive place in therapy of Benadryl, Pyribenzamine, and Anthallan can be appraised.

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THE THERAPEUTIC USE OF RADIOACTIVE ELEMENTS IN MALIGNANCY *

By P. F. HAHN and C. W. SHEPPARD, *Nashville, Tennessee*

DURING the past year there have been numerous allusions to the rôle to be played in medicine by the developments in atomic fission. The uninitiated reader might infer that such applications are something solely to be looked for in the future, contingent on a considerable amount of developmental research. There is no need to argue the need for fundamental investigation in this field. The need will always exist regardless of our progress. However, for the better part of 10 years, methods and tools of nuclear physics have been applied to medicine. In general, this application has been in two directions. First, isotopes offer much promise in solving the mysteries of metabolic processes in the animal and human body. Second, the artificially produced radioactive isotopes have opened up such broad horizons in the treatment of malignant disease that they will ultimately in all likelihood far surpass x-ray and radium together in therapy.

The metabolic use of isotopes and their diagnostic applications embrace such wide fields in physiology, biochemistry, medicine, surgery and biology that volumes could be written about the progress which has been made in the past decade. Probably no single new tool has had such a far-reaching influence on medical science or caused more concepts to be altered.

Comparatively little attention has been paid to the numerous possibilities for research in the therapeutic use of isotopes. It is with this field that we shall deal in this communication.

Up to recent months the chief and nearly sole source of isotopes was the cyclotron. As a result relatively few clinical investigators had access to artificial radioactive material for study. Due to the limited supply, attention was directed largely to the use of a few of the most available cyclotron produced isotopes. Radioactive phosphorus is one of these and has been employed in the treatment of a variety of diseases. The chain reacting uranium pile now presents a new and prodigious source of isotopes.

Below we list what appear to us to be the criteria for therapeutic usefulness of radioactive isotopes:

1. The "half-life" must not be too long. Neither should there be an associated component of long half-life or a long-lived contaminant whose separation is difficult or impossible to effect. Such long-lived materials prevent good control of the supplied radiation and also might prove ultimately

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From the Laboratories of Cancer Research, Meharry Medical College, and the Department of Biochemistry, Vanderbilt University, School of Medicine, Nashville, Tennessee.

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to be carcinogenic in themselves. We have arbitrarily set about 10 days as the upper limit of half-life which is desirable from this point of view.

2. The half-life must be sufficiently long that the isotope can perform its work. This is important also since it is generally felt that the continuous delivery of radiation has advantages over delivery of a short burst of more intense radiation. Lower limits of half-life must for the present be dictated by shipping facilities and we have felt that two days represents the minimum at this time unless one is very near the source of material. Later it may be possible to use some of the isotopes with shorter half-lives to great advantage and this restriction is therefore purely temporary. However, as shorter half lives are used increasingly high activities are required for a given effect thus presenting technical problems in the maintenance of radiation safety for the operator.

3. The biological behavior of the material to be used should be well established since its effectiveness from a standpoint of localization is involved.

4. The chemistry of the element to be used must be well understood. Isotopes of some of the rarer elements which are now difficult to obtain in pure form with convenience may later have practical value.

5. The radiation spectrum of the isotope should be established and proper cognizance of the relative beta and gamma radiation which it is desired to deliver to tissue taken into account. If a hard gamma ray is emitted, proper shielding in shipment and in the laboratory becomes more difficult.

6. The radioactive material should preferentially be deposited selectively in the tissues it is desired to treat.

7. If the isotope is toxic, specific activity becomes important in keeping the dosage of material well under toxic limits.

8. The cost of producing and shipping the isotope is of great importance and will take on added significance as the use of isotopes in therapy becomes more widespread.

In table 1 are listed a number of isotopes culled from Seaborg's table¹ which lists some 450 known radioactive isotopes. The list in table 1 was made with several objects in mind. In general the criteria discussed above were considered to be limiting factors. In several instances isotopes were listed in order to point out how most of the criteria could be satisfied but one or more of these might limit the use of that particular isotope either now or perhaps forever. The most striking observation is the paucity of isotopes which hold promise of use as therapeutic agents. There are only about a half dozen which deserve critical investigation and appraisal at this time. Later the list may be increased slightly in length as it becomes feasible to utilize some of the shorter lived materials.

Let us consider the advantages and disadvantages of this small group in some detail. In the treatment of certain diseases the radiological therapist has found that "spray radiation," i.e. generalized x-radiation over the whole body is of value. Under such conditions a comparatively long continued low grade radiation might have advantages over a short exposure to a more

TABLE I

Isotope	$\frac{1}{2}$ Life	Long-Lived Contaminants	Specific Activity*	Chemical Knowledge*	Knowledge of Biological Behavior*	Radiation	Yield	Comment
Na ²⁴	14.8 hr.	None	B	A	A	Hard β^- and γ	A	Very heavy lead protection required
P ³²	14.3 d.	None	A	A	A	β^- only	A	Half-life slightly too great
K ⁴²	12.4 hr.	None	C	A	A	Very hard β^-	A	Of doubtful present biological use
Mn ⁵²	6.5 d.	Mn ⁵⁴	A	A	B	β^+ , K and hard γ	A	Long-lived contaminant, heavy lead protection
Cu ⁶⁴	12.8 hr.	None	B	A	B	β^- , β^+ , K, no γ	A	Use limited by short half-life
Ga ⁷²	14.1 hr.	None	C	B	D	Hard β^- and γ	B	Not therapeutically promising
As ⁷⁶	26.8 hr.	None	C	A	B	Very hard β^- and γ	B	Low specific activity for toxic element
Br ⁸²	34 hr.	None	C	A	B	Medium β^- and γ	B	Half-life rather short
Kr ^{79, 81}	34 hr.	None	C	A	B	β^+ only	C	A radioactive inert gas
Y ⁹⁰	60 hr.	None	C	B	C	Very hard β^- only	B	Further biological study required
Mo ⁹⁹	67 hr.	None	C	A	C	Hard β^- , medium γ	B	Further biological study required
Ag ¹¹¹	7.5 d.	None	A	A	B	β^- only	B	A promising pure β ray emitter
I ¹³⁰	12.6 hr.	None	A	A	A	Medium β^- and γ	A	A good cyclotron isotope for therapy
I ¹³¹	8.0 d.	None	A	A	A	Medium β^- and γ	A	A good pile isotope for therapy
La ¹⁴⁰	40.0 hr.	None	B	C	D	Hard β^- and γ	B	Further biological study required
Au ¹⁹⁸	2.7 d.	None	A	A	B	Medium β^- and γ	A	A good therapeutic isotope
Au ¹⁹⁹	3.3 d.	None	A	A	B	Medium β^- and γ	B	Very high specific activity possible
Bi ²⁰⁷	6.4 d.	None	A	A	B	Medium γ , K?	B	Production limited to cyclotron yield

* The classification is as follows: A—good; B—fair; C—poor; D—very poor.

intense source of radiation because of the suspected increased susceptibility of cells during mitosis. Actually such a feature of relatively constant low grade radiation, which presents practical economic difficulties to those using x-ray, is one of the chief advantages which isotope therapy has to offer. Sodium in ionizable form is uniformly distributed in the extra-cellular water of the body some hours following the administration of NaCl orally or by vein.² Evans and Quimby³ have compared the effects of "spray radiation" by means of x-rays with that obtained by the use of NaCl in mice and have found that the results were similar. The chief advantage in the use of Na²⁴ isotope here would be the possibility of extending the radiation period for many hours. On the debit side is the difficulty of shipping and handling the sodium isotope because of the exceptionally hard gamma ray emitted.

A great deal has been written concerning the use of P³² as a therapeutic agent and this has best been summarized by the report of Reinhard, Moore, Bierbaum, and Moore.⁴ They conclude that success in its use has been most conspicuous in the treatment of polycythemia vera and possibly in myelo-

genous leukemia. We have already expressed ourselves as being not in favor of use of isotopes in treatment of polycythemia except under unusual conditions since phlebotomy is much simpler, without hazard to the patient, and quicker in its action.⁵ If the usefulness of P^{32} in treatment of myelogenous leukemia is due to the semi-specific action on the bone marrow it seems reasonable to expect that one of the other isotopes discussed below might be more advantageously employed. We also feel that the half-life is too long, making a "titration" of the administered radiation difficult. It would seem that the widespread use of P^{32} has been based largely on its availability as a cyclotron product, and that it should soon have competitors under the new pile economics.

Use of manganese (Mn^{52}) would be feasible if only a single or several treatments were necessary since then the inclusion of about 1 per cent of the long-lived accompanying component (Mn^{54}) would be relatively unimportant. However, experience^{6, 7} has shown that patients with malignancies of the lymphoid system usually require repeated treatment and it must therefore not be included in the armamentarium of isotopes useful for such therapy.

Cu^{64} is a good example of an isotope which may at some time in the future offer possibilities in therapy. It is an element closely associated with certain enzyme systems and is somewhat selectively taken up by certain tissues. However, its short half-life precludes its widespread successful use at this time due to difficulties in shipping and prompt use.

As^{74} presents an example of a debatable element for inclusion in a list of therapeutic agents. Because of its toxicity the low specific activity is against its use. However it possesses some degree of selectivity in deposition in tissues; large amounts are commonly administered in anti-syphilitic therapy; all in all more study should be devoted to its possibilities before condemning it.

Yttrium⁹⁰ differs from its neighbor strontium only in possessing a single 4d electron in an interior N shell and thus has similar chemical properties. It should be studied to see if it behaves similarly to strontium in replacing some of the body's metabolic calcium. Its hard pure beta particle spectrum should make it an exceedingly useful substitute for P^{32} or long lived strontium in the treatment of diseases of the bone and marrow such as myelogenous leukemia, Ewing's tumor, and bone sarcomata.

Ag^{111} has not yet been tried, but affords room for much speculation as a possible material for use topically or by direct injection because of its propensity to attach itself to protein and remain in situ. It is a pure beta emitter and its radiation would be well localized.

I^{130} and I^{131} have been investigated fairly thoroughly and will probably play an increasing rôle in handling of certain diseases of the thyroid. It is representative of superb biological selection which is an aim to be set for the use of most isotopes.

Au^{198} has only recently been tried as a therapeutic agent^{8, 9, 16} and it is too early to determine its full value or future in therapeutic use. It has many

of the desirable characteristics and was selected as having the most promise from a standpoint of satisfying the criteria delineated above. In addition it is easily made in pure form without any trace of discernible contaminant isotope. Its chemistry is unique and well understood. Its insolubility as a metal allows it to be injected with reasonable assurance that it will stay at the site of injection, when given subcutaneously or intramuscularly. It is not subject to excretion when administered as the metal and therefore does not give rise to problems of radioactive excreta or loss from the body with accompanying lowered efficiency and uncertainty as to dosage. Theoretically it should be more useful than radium in local radiation of tissues since it can be infiltrated throughout the affected area. Thus it is not necessary to establish highly local sites of intense radiation with concomitant lack of radiation to adjacent areas not accessible to direct radium application. Furthermore, it is not necessary to remove the material injected thus allowing infiltration freely during operative procedures.

We now turn from a consideration of possible isotopes to an outline of a few suggested technics in therapeutic use. Some of these have received preliminary study but a number have not yet been tried and certainly bear investigation.

- I. For general body radiation to correspond to spray x-radiation.³
 1. Na^{24} has been used for this purpose since it is generally distributed in the total body water.
- II. Utilization of the peculiar affinity of a tissue for a given isotope in order to obtain localized radiation.
 1. $\text{I}^{130, 131}$ and its use in therapy of hyperthyroidism and thyroid tumors.^{10, 11, 12}
- III. Utilization of chemical affinity of tissue for an element and substitution of another element which behaves similarly physiologically but has a more suitable spectrum, half-life or other characteristic, or which is more readily available.
 1. Sr^{85} as a substitute for calcium, there being no suitable Ca isotope for therapy of metastatic bone tumors.¹³ Its disadvantage is the 55 day half-life. Yt^{90} may be found to provide an even better substitute. However, its biological distribution must first be studied.
- IV. Utilization of the semi-specific uptake of elements by tissues where some degree of generalized radiation is either desirable or not strongly contraindicated.
 1. P^{32} in therapy of myelogenous leukemia and polycythemia vera.⁴
- V. Utilization of specific functions of certain tissues in their physico-chemical behavior toward administered materials.
 1. Phagocytosis of intravenously administered particulate material in concentrating radiation in the reticulo-endothelial system. Radioactive particles of gold, manganese dioxide, and chromic phosphate have been used for selective radiation of this system;

especially the liver and spleen, in the leukemias, Hodgkin's disease, lymphoma, and other disorders.^{6, 8, 14}

2a. Intraperitoneal injection of colloidal material for removal by abdominal lymph nodes in diseases such as lymphoma and abdominal Hodgkin's.¹⁶

2b. Intrathoracic injection of colloidal material for removal by mediastinal and hilar nodes in pulmonary tumors and metastatic involvement of the thorax.

3. Utilization of chemo-tactic properties of the system to obtain localization, e.g. at the site of inflammatory processes. The behavior of certain dyes in this respect suggests the use of attached isotopes.

VI. Topical application of isotopic material in therapy of superficial lesions.

1. Preliminary studies using P^{32} as reported by Low Beer.¹⁵

2. Preliminary studies using colloidal Au^{198} and $Ag^{111}NO_3$.¹⁶

VII. Treatment of tumors of the hollow viscera by instillation of radioactive materials to obtain radiation by proximity.

1. Therapy of bladder tumors by instillation of suspension of radioactive material in non-absorbable form, e.g. colloidal Au .¹⁹⁸

1a. Instillation of material which would readily bind itself to mucosal surface affording localization to a higher degree, e.g. $Ag^{111}NO_3$.¹⁶

2. Instillation of jelly containing isotopic material in uterine cervical tumors.

3. Retention enema therapy of carcinoma of rectum or colon.

4. Localized radiation of the involved area in carcinoma of stomach.

a. Use of the double lumen Miller-Abbott tube to plug the pylorus. Installation of a short-lived isotope in insoluble form. Adjustment of position of patient under the fluoroscope in order to cause pooling at the desired site. Withdrawal and rinsing of the solution from the stomach at desired time.

5. Localized radiation of selected segments of the intestinal tract.

a. Use of the three lumen Miller-Abbott tube with distal and proximal balloons. Suspended material in unabsorbable form is mixed with a small amount of barium and introduced into the third lumen to fill the interspace. It is then pumped and rinsed after a desired interval of time.

VIII. Selective therapy of specific organs or tissues making use of specific action of certain drugs to manipulate the progress of the isotopic material.

1. Radiation of the spleen alone or at least with minimal radiation of other parts of the lymphoid system. The subject is nembutalized to cause engorgement of the spleen and its temporary physiological removal from the phagocytic system. Injection of a moderately large, semi-blocking dose of non-radioactive colloidal material, such as Trypan blue, or colloidal carbon. Administration of a small amount of epinephrine to contract the spleen. Administration of

colloidal radioactive preparation by vein for phagocytosis by the spleen.

IX. Therapy of pulmonary carcinoma by direct inhalation of radioactive material.

1. Use of an isotope prepared as an aerosol.
2. Direct use of a radioactive gas such as Krypton.

It is difficult to evaluate either of these procedures until further studies have been made.

X. Direct radiation of discrete masses of tumor tissue by infiltration of the tumor with an inert, insoluble isotopic material such as Au^{198} or Ag^{111} .¹⁶

XI. Physical manipulation in localization of the distribution of radioactive material.

1. In the therapy of leukemia one of the limiting factors in the administration of sufficient radiation therapy with isotopes is the possibility of induction of leukopenia and thrombocytopenia by irradiation of the bone marrow. This might be partially avoided by occluding the circulation to the extremities prior to the intravenous administration of material to be removed from the circulation (see V. 1). Since disappearance from the circulation is very rapid the blood stream should be satisfactorily cleared of the therapeutic material within a short time and circulation might then be restored. In this way the marrow of the long bones may be available to furnish leukocytes and platelets during the period when maximum cellular destruction of the other marrow was taking place. When the marrow of the head and trunk had recovered its ability to produce cellular elements, the long bones could be treated by x-ray.

We do not wish to suggest that all of the possibilities which we have listed above are well enough established to justify their immediate use. Some of the technics have been given clinical trial and have shown themselves to be feasible. Others offer sufficient promise that they might shortly be applied in medicine with little additional developmental research. A few are sufficiently controversial that they require considerable additional analysis. Experience has shown that during the investigation of the feasibility of methods of radiation therapy enough basic information is usually obtained to justify the effort even when a negative result is encountered.

Some may argue that we are not prepared to begin the therapeutic use of isotopes on a large scale until more is known concerning the unfavorable side reactions produced by radiation and the possible untoward end results which might accrue from their use. It is true that there should be no indiscriminate use of these materials. They must be placed in cautious and competent hands. Furthermore one must be hesitant to use radiation in any form in the treatment of any disease which runs a benign course. However, there

is every reason to proceed with vigor in attacking those malignant conditions in which the prognosis is poor even though our knowledge is incomplete at the moment. If we were to wait 10 more years on the assumption that the necessary fundamental background could be built up in that time, there would have been many hundred thousands more victims of malignancy who might have been helped to some degree, barring some revolutionary new form of therapeutic approach to this problem not in sight at this time. If the outlook for continued life in such a disease is but a few months, one is perfectly justified in taking some risk in treatment when there is every reason to believe that a certain percentage of the patients may obtain some relief and some may have many years added to their lives.

The fiftieth anniversary of the use of roentgen-rays has recently been celebrated. Certainly in the first 30 years of their use, many mistakes were made. The hazard involved in the use of this tool, however, did not preclude its widespread application in the treatment of malignant disease. It should not be said that with the wider range of radiation spectra available and the resultant increased complexity of the underlying problems facing us, we should hesitate to embark on the productive use of these extremely valuable and now available agents. Their flexibility suggests a multitude of uses. It is to be hoped that they will be used widely but wisely.

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THE INHALATION OF DUST PENICILLIN *

By LOUIS KRASNO, Ph.D., M.D., MARY KARP, M.D., PAUL S. RHOADS, M.D., F.A.C.P., *Chicago, Illinois*

IN view of the favorable reports in recent literature on the inhalation of therapeutic agents, especially penicillin, and because of the many possibilities of the method, we have attempted to produce even greater and more protracted topical effectiveness by a method which involves the inhalation of fine dust aerosol particles. This method has simplified the mechanics of aerosol therapy, thus expanding its scope more readily for office and home treatment.

Aerosols may be defined as suspensions of liquids or solids in air or oxygen. In the past, the aerosolization methods have included only the inhalation of suspensions of liquids. The method described in this paper will be referred to as the inhalation of dry dust penicillin, thus distinguishing it from the former penicillin vapor method.

The apparatus used for inhalation therapy in the past has been based on the delivery of the aerosol vapor under positive pressure of oxygen or air by means of a hand bulb, oxygen tank and gauge, or compressed air machine. The principle utilized in the new method is based on the negative pressure created by normal breathing during the inspiratory phase. Inhaling penicillin dust in this manner is more physiological and permits an even, and perhaps a wider distribution of medicament throughout the respiratory tract. The patient is not required to manipulate an exhaling valve during the expiration phase, and the cumbersome equipment of oxygen tank and gauge is unnecessary. The inhalation of the dust particles of penicillin yields greater effect than the vapor because there is greater concentration of penicillin per unit area and because the penicillin must go into solution while in contact with the mucous membrane before it can be absorbed.

The penicillin dust used in this experimental study was Crystalline Sodium Penicillin, processed to number 100 mesh particles.† The crystalline form was found to be less hygroscopic than the amorphous sodium penicillin salt and could be stored at room temperature without losing its potency more readily than the penicillin liquid, which is used as the nebulin for the vapor method.

There were a number of objectives which this study attempted to achieve. They were: 1. To determine whether penicillin as a fine dust has any irritating qualities or will give rise to untoward effects when inhaled. 2. To develop a simple and efficient practical device for the inhalation of penicillin

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From the Division of Surgery, Northwestern University Medical School and Department of Anesthesiology, Wesley Memorial Hospital (Dr. Karp). From the Division of Medicine, Northwestern University Medical School (Dr. Rhoads, Professor of Medicine).

† The penicillin for this study was especially processed by, and furnished through the courtesy of Abbott Laboratories, North Chicago, Illinois.

dust, which would lend itself to home and office use. 3. To determine the effectiveness of this method upon the bacterial contents of the nose, throat and sputum in patients with varying types of respiratory infections. 4. To determine the rate and degree of absorption of the medicament into the systemic circulation. 5. To evaluate the effectiveness of the method as compared with the vapor aerosol inhalation method and other known routes of penicillin administration.

APPARATUS

The apparatus was designed in terms of the aforementioned objectives, namely,

1. To deliver penicillin as a fine, nonirritating dust to respiratory tract.
2. To have a simple, efficient and practical mechanical device for use at home, in the office, and in the hospital.

The apparatus now being used represents numerous modifications of the original device * since penicillin dust possesses certain qualities which do not lend themselves to ordinary technics. Penicillin is highly electrostatic, easily adhering to surface areas. In addition, it is hygroscopic and goes into solu-

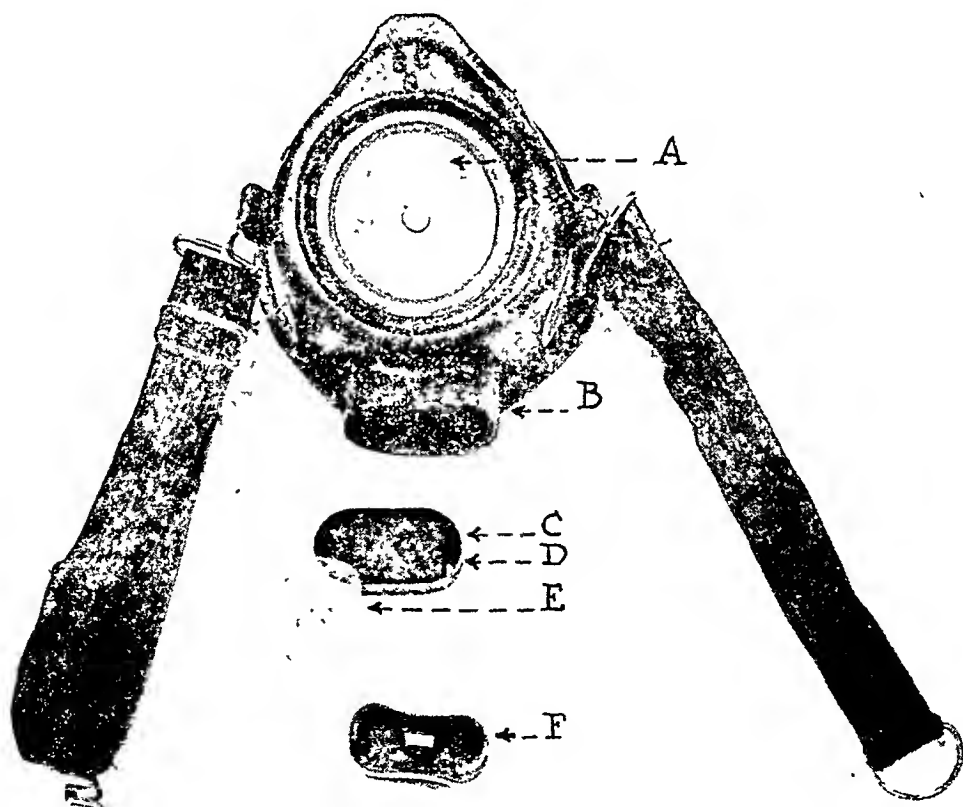


FIG. 1. Mask used for the inhalation of dust penicillin.

* The present mask was kindly fabricated by the Chicago Eye Shield Company, according to the specifications of one of the authors (Krasno).

tion readily. The technic finally developed allows the penicillin to be released easily as a dust and at the same time precludes the moisture of exhalation from dissolving it.

The device consists of an oro-nasal face piece which is held on the face by an elastic head band (figures 1 and 2). The front of the mask contains a



FIG. 2. Mask assembled and applied to patient's face.

large exhalation valve (A) in direct line with the stream of exhaled air. The portion of the mask about the chin contains a rubber sleeve (C) fitted with an inhalation valve (B) which directs the inhaled air in the plane at right angles to the stream of exhaled air. The inhalation valve contains a special detachable metal chamber (D) containing the penicillin dust. The penicillin chamber is fixed with a fine wire mesh (E) which is covered with a finely perforated cellophane paper (F). It has been found that penicillin dust is essentially non-adherent to cellophane. The penicillin dust is placed on top of this platform. During the inhalation, air is drawn through the per-

forations of the penicillin chamber and the dust is released, passing through the inhalation valve and into the respiratory passages. The penicillin dust is protected from the moisture of exhalation by the one-way inhalation valve and by the fact that the exhaled air is conducted through a plane at right angles to the inhaled air. There is a small hole (H) about 6 mm. in diameter on top of the mask just above the end of the nose. This allows a substantial amount of air to be drawn in easily and avoids any resistance on inspiration. This supplementary inlet for air is also necessary to keep the amount of penicillin dust inhaled in optimum quantities.

EXPERIMENTAL PROCEDURE

Sixty-six subjects, 36 males and 30 females, were used in this experiment.* The age variation was from 7 to 72 years. The subjects were divided into three groups. The first group consisted of four experimental subjects (including the authors) on whom any irritating properties or untoward effects of inhaling penicillin dust would be detected. The second group comprised 23 patients who were hospitalized for various types of respiratory diseases. The third group consisted of 39 ambulatory patients who came to the office or hospital for penicillin treatment.

Throat, nose and sputum cultures were obtained on the experimental subjects prior to the inhalation of 100,000 or 200,000 units of penicillin and at one and two hours following inhalation. Blood levels were obtained on various subjects in this group. All hospitalized patients received 100,000 units of penicillin dust by inhalation for 20 minutes three times a day. All treatments followed meals to reduce the possibility of washing down the penicillin from the pharynx into the stomach. Throat and nose cultures prior to first treatment and daily cultures thereafter were taken on all hospitalized patients. Preliminary and follow-up sputum cultures were obtained in all cases of bronchiectasis. Blood levels were made on various patients. The clinical progress was followed by the patient's doctor and the authors. The duration of therapy was determined clinically and bacteriologically for each case.

The majority of the office patients were given one treatment of 100,000 units of penicillin, an occasional patient receiving more than one treatment. The symptoms, duration of symptoms and physical findings were noted prior to inhalation, and 24 hours after the treatment was given. It was not practical to obtain cultures on this group, but the data accumulated from these office patients served to give further information regarding the course of symptoms and allergic aspects as influenced by this type of treatment.

RESULTS

Table 1 lists the type of pathological conditions for which these patients were treated. The greater portion had upper respiratory tract infections,

* The observations reported here cover a period extending from October 1946 to February 1947 inclusive. The results obtained since that time are essentially the same as reported

TABLE I
Clinical Diagnosis of Cases Treated

Clinical Diagnosis	No. of Cases
I. Upper respiratory infections	
a. Common cold (acute rhinitis and/or acute nasopharyngitis)	46
b. Chronic nasopharyngitis	4
c. Chronic sinusitis	3
d. Laryngotracheal bronchitis	2
II. Lower respiratory infections	
a. Bronchiectasis	6
b. Chronic bronchitis	2
c. Bronchial asthma with chronic bronchitis	1

TABLE II
Summary of Bacteriological Data: Throat Cultures

Organism	Pre-therapy Growth			Post-therapy Growth			No Growth
	Heavy	Mod- erate	Slight	Heavy	Mod- erate	Slight	
1. α hemolyticus streptococci (<i>Str. viridans</i>)	17	12	1	1	4	9	16
2. β hemolyticus streptococci (<i>St. hemolyticus</i>)							
3. Diplococcus pneumococci	1	10					11
4. γ streptococcus anhemolyticus		4			2		2
5. <i>Staphylococcus aureus</i>	1	10	3		7	3	4
6. <i>Staphylococcus hemolyticus aureus</i>	1	4					5
7. <i>Staphylococcus albus</i>	5	17	2		10	4	10
8. <i>Neisseria catarrhalis</i>		11	2		6	4	3
9. <i>Micrococcus tetragenous</i>		3					3
10. <i>Aerobacter aerogenes</i>		1				1	0
11. <i>B. hoffmannii</i>		3				1	2
12. Diphtheroids		2				1	1

Numerical values represent number of cases.

TABLE III
Summary of Bacteriological Data: Nose Cultures

Organism	Pre-therapy Growth			Post-therapy Growth			No Growth
	Heavy	Mod- erate	Slight	Heavy	Mod- erate	Slight	
1. α hemolyticus streptococci		2					2
2. β hemolyticus streptococci		1					1
3. Diplococcus pneumococci							1
4. γ streptococcus anhemolyticus		1					1
5. <i>Staphylococcus aureus</i>		2					2
6. <i>Staphylococcus aureus hemolyticus</i>		3				1	
7. <i>Staphylococcus albus</i>		7	4		1	2	8
8. <i>Neisseria catarrhalis</i>		1	1				2
9. <i>B. proteus vulgaris</i>		1					1

Numerical values represent number of cases.

39 of which had symptoms of the "common cold," such as acute rhinitis, lacrymation, nasopharyngitis and general malaise.

It can be seen from tables 2, 3, and 4 that the inhalation of dry penicillin quickly causes the reduction or disappearance of gram positive bacteria and

in the massive doses used seems to influence some of the gram negative bacteria. This is accomplished readily, often in one treatment. Penicillinase has been added to the laboratory specimens without changing the bacteriological results.

BACTERIOLOGICAL DATA ON THROAT CULTURES

Table 2 illustrates the effect of dry penicillin therapy on the various types of organisms found in the throat. The table is arranged according to the extent of the growth of a given organism before and after course of therapy. It is interesting to note that all of the organisms, including the gram negative

TABLE IV
Summary of Bacteriological Data: Sputum Cultures

Organism	Pre-therapy Growth			Post-therapy Growth			No Growth
	Heavy	Mod- erate	Slight	Heavy	Mod- erate	Slight	
1. α hemolytic streptococci (<i>S. viridans</i>)	6	5				4	7
2. β hemolytic streptococci		2					2
3. Diplococcus pneumococci		1	2				3
4. γ streptococcus anhemolyticus		2			1		1
5. <i>Staphylococcus aureus</i>	3	3			2	2	2
6. <i>Staphylococcus albus</i>	1	5			5		1
7. <i>Neisseria catarrhalis</i>		3	1		2	2	
8. <i>Micrococcus tetragenus</i>		1					1
9. <i>B. mucosus capsulatus</i>		2					2
10. <i>Neisseria pharyngis sicca</i>			1				1

Numerical values represent number of cases.

bacteria, were appreciably influenced by the treatment. Prior to inhalation of penicillin dust 14 patients had a heavy growth of *Streptococcus viridans*, 10 showed a moderate growth, and one had a slight growth. After a course of treatment, there was one instance of heavy growth, four of moderate growth, seven showing slight growth, and 13 with no growth evidenced after 72 hours of incubation on blood agar plates. In the cases with *D. pneumoniae*, there was one of heavy growth, 10 with moderate growth before inhalation of dry penicillin. After therapy the *D. pneumoniae* disappeared in all 11 patients.

BACTERIOLOGICAL DATA ON SPUTUM CULTURE

Table 4 illustrates the effects of the treatment on the sputum specimens. Before therapy six cases showed a heavy growth of *Streptococcus viridans*, and five a moderate growth. After inhalation of dry penicillin there was a slight growth in four and no growth in seven cases, one patient exhibited a moderate growth of *D. pneumoniae* and two a slight growth, which disappeared in each instance following therapy. In two cases there was a mod-



FIG. 3. Blood agar plates. (a) demonstrates growth of bacteria from throat culture before inhalation treatment and shows heavy growth of small colonies producing green hemolysis (*Streptococcus viridans*). (b) Blood agar plate of throat culture taken two hours after inhalation of 100,000 units of penicillin. Reported no growth 72 hours.

erate growth of *Streptococcus hemolyticus* which completely disappeared after inhalation treatment.

CLINICAL EVOLUTION OF RESPONSE TO DRY PENICILLIN THERAPY

Table 5 represents the symptomatic improvement of the 39 patients treated at the hospital as judged by the patient himself, the attending doctor and the authors. Ten cases were rated a two plus improvement, 15 a three plus improvement, and 14 a four plus improvement.

A study of the data on six bronchiectatic patients revealed less cough and secretion in these patients on dismissal. The patient with bronchial asthma

TABLE V
Results in the 23 Hospital Patients

Clinical Diagnosis of Cases	Clinical Results			
	+	++	+++	++++
I. Upper respiratory infections				
a. Common cold (acute rhinitis and/or nasopharyngitis)		3	8	10
b. Chronic nasopharyngitis		1	2	1
c. Chronic sinusitis		2	1	
d. Laryngotracheal bronchitis				2
II. Lower respiratory infections				
a. Bronchiectasis		3	3	
b. Chronic bronchitis		2		
c. Bronchial asthma with chronic bronchitis			1	

Clinical results expressed in one, two, three or four +.
Numerical values represent number of cases.

and chronic bronchitis had marked improvement, the infectious condition almost completely disappearing, although the allergy persisted to a decreased degree. The two patients with chronic bronchitis showed a moderate improvement.

It was in the acute conditions of the upper respiratory tract that the best results were obtained. Over 90 per cent of the 23 patients with upper respiratory tract infections treated at the hospital had marked improvement in their symptoms. Those patients with acute rhinitis and laryngo-tracheo bronchitis had recovered within one to three days. "The common cold syndrome" of acute rhinitis, lacrimation, naso-pharyngitis, and general malaise responded to the inhalation therapy; eight cases were listed as three

TABLE VI
Office Patients

Patients	Cough	Fever	Rhinitis	Sore Throat	Chest Pain	Earache	Headache	Malaise	Duration of Symptoms				Number of Treatments	Response to Treatments
									Days	Wks.	Mos.	Yrs.		
1	+			+			+	+		3			1	+++
2**	+			+					2	1			1	+
3	+		+	+			+	+		1			1	++
4	+		+	+							1		1	+++
5	+		+	+						3			1	+++
6	+		+	+	+		+	+	5				1	+++
7*	+			+			+	+				14	1 per week	+++
8	+		+	+			+	+	6				1	+++
9	+	+	+	+			+	+	5				1	+++
10**				+		+	+	+	3				1	++
11	+	+	+	+			+	1	4				1	+++
12	+	+	+		+		+			1			1	+
13	+			+						1			1	++
14	+		+	+					5				1	+++
15	+		+	+			+	+	4				1	+++
16	+		+				+	+		1			1	++
17*	+											10	1 per week	+++
18	+											4	1 per week	++
19	+		+	+					4				1	+++
20	+	+	+	+	+				3				1	+++
21	+				+							1	1 per week	++
22							+					5	1 per week	+++
23	+				+							3	1 per week	+++
24**	+		+	+					2				1	++
25	+		+	+					10				1	+++

* Ambulatory bronchiectatic patients.

** In these cases, the immediate response was minimal but the patient felt much better 2 to 3 days thereafter.

plus improvement and 10 as four plus or complete improvement. Three had moderate or two plus elimination of symptoms.

Twenty-nine of 39 cases treated at the hospital (75 per cent) had only one treatment, six had two inhalations, and three had four treatments. The remainder had four to 18 inhalations, the highest number being reserved for the chronic bronchitis and chronic sinusitis patients. The patients with

diseases of the lower respiratory tract had from 10 to 18 treatments, administered in four to six days.

It is singular that to the present time and including 66 cases there has been noted no sensitivity reaction to the penicillin. With the vapor aerosol method, transient fever, dyspnea or dermatitis has occurred in 4 to 20 per cent of the cases, depending upon the concentration of the drug used.*

Table 6 lists the duration of symptoms prior to the treatment and degree of improvement within 24 hours in a group of office patients treated with dry penicillin.

Penicillin assays of urine and blood were determined by Fleming's modification of the Wright slide cell technic.¹ Defibrinated sheep blood was used instead of human blood and the results were read directly from the test tubes without the use of slides. Single blood determinations were made on patients in the hospital and penicillin blood curves were established.

Table 7 illustrates the results of the penicillin assays of the blood and shows values from .03 to 1.92 units per cubic centimeter. Blood level curves would indicate a slow absorption, the maximum level being obtained 3 to 3½ hours after the inhalation.

COMMENTS

It is difficult to evaluate therapeutic results in a preliminary report. Records of clinical improvement as judged by patient and doctor have no more value here than in any other clinical study. However, we are in the process of running controls in the form of patients treated by other methods. The positive findings in the report are the definite, though perhaps temporary, changes in bacterial flora,† and the appreciable penicillin blood levels obtained. The duration of the change in bacterial flora has not been determined but the clinical improvement in many instances has been more than temporary. The clinical improvement is definite and further work is being carried out to investigate the duration of results. The main purpose of this preliminary report is to present a new method of administering penicillin. The method appears to offer more effectiveness in ridding the upper respiratory tract of gram positive bacteria than other aerosol methods. Appreciable blood levels would indicate the protracted, effective absorption offered by this method, and the possible use of inhalation treatment for systemic conditions other than those of the respiratory tract. This method would appear to have a definite value in initiating the process of ridding the respiratory tract of pathogens, but it may be necessary to supplement the process with intramuscular penicillin administration and with other medications. In other instances its value may be adjunctive rather than primary.

* Since the writing of this paper there has been one case of contact dermatitis allergy, manifested by an herpetiform-like rash in the skin area of nose and mouth. The dermatitis has reappeared in this patient on each attempt to repeat the penicillin inhalations.

† We wish to make it clear that pathologic significance is not attributed to all the bacteria listed in the tables, e.g. *Streptococcus viridans* in throat cultures.

TABLE VII
 Penicillin Assays (Units per c.c. of Blood) from Blood Samples Drawn at Varying Intervals Following Inhalation Treatments

	Amount of Drug Inhaled	Age of Patient	Interval in Minutes										Interval in Hours			Misc.		
			15'	30'	60'	90'	120'	150'	180'	210'	240'	270'	300'	420'	24 hrs.		30 hrs.	48 hrs.
1	100,000 units	30	0	0	0	0	0	0	.24*	.24	.12	0						urine assay = 30.72 u./c.c. after 2nd inhal.
2	200,000 units	54	.03			.06			.03**	.03	0	0		.16		.03	0	
3	200,000 units	30			0		0		0	.06*								
4	100,000 units	28	.03		0		0		0									
5	100,000 units	2		1.92														
6	100,000 units	16	0	0	.06													
7	100,000 units	45							.48*	.12	.03	.48						

* Subsequent treatments of 100,000 units.

** Subsequent treatments of 200,000 units.

CONCLUSIONS

1. A method is presented for the administration of penicillin dust by inhalation.

2. The data given show that there is a marked diminution of gram positive bacteria of the upper respiratory tract following the treatments. Coincident with the treatment there is improvement in signs and symptoms of upper respiratory tract infections and bronchiectasis.

3. In many instances effective blood levels were demonstrated, usually, 3 to 3½ hours after inhalation.

4. The method appears to be more effective than other methods of inhalational penicillin therapy and causes fewer side reactions.

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SPONTANEOUS MEDIASTINAL EMPHYSEMA AND SPONTANEOUS PNEUMOTHORAX—A REPORT OF 20 CASES *

By HELEN A. DICKIE, M.D.,† *Madison, Wisconsin*

THE rapidly increasing number of case reports indicates that spontaneous mediastinal emphysema is not rare.¹⁻¹² Further case reports are essential to establish the frequency. The occurrence of spontaneous mediastinal emphysema, spontaneous pneumothorax and a combination of these two conditions among the students seen at the University of Wisconsin Student Health Service from March 1943 to March 1947 is reported for two reasons: first, because spontaneous pneumothorax is no longer considered a medical rarity and some estimations of its frequency have been recorded; second, and more important, to stress the frequency in which the two conditions are associated. In this way a clearer idea of the frequency of mediastinal emphysema may be gathered.

The actual incidence of spontaneous pneumothorax is difficult to establish, although numerous series have been reported.¹³⁻¹⁶ In a recent report by Schneider and Reissman¹⁸ the authors state that a verified history of spontaneous pneumothorax was given by about one in 500 men in a group of selectees in the 18 to 38 age group. Heath¹⁹ reports 10 cases of spontaneous pneumothorax in a survey of 28,000 admissions to the A. A. F. Regional Hospital in Lincoln, Nebraska. These were all confirmed by roentgen study. Blackford²⁰ reports the incidence of spontaneous pneumothorax to be about one in 1000 among college students at the University of Virginia.

The usual explanation given for the production of spontaneous mediastinal emphysema is that the source of the air is from a ruptured alveolus or alveoli. From this site within the lung the air dissects along the perivascular sheath to the mediastinum. In Macklin's^{21, 22} experiments with cats the associated pneumothorax was caused by a rupture of the mediastinal pleura with the resultant escape of air into the pleural spaces. The frequency of pneumothorax associated with mediastinal emphysema would indicate that this mechanism occurs in the majority of the spontaneous pneumothoraces seen in otherwise healthy individuals.²² The reason for the overdistention and rupture of the alveolar wall in these patients is not understood. As a rule there is no history to suggest increased intrabronchial pressure immediately preceding the onset.

• If this explanation be correct, then mediastinal emphysema should occur more frequently than spontaneous pneumothorax and the two conditions

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From Department of Preventive Medicine and Student Health, University of Wisconsin, Madison, Wisconsin.

† Associate Professor of Preventive Medicine, University of Wisconsin.

should be associated frequently. The failure to demonstrate free mediastinal air in a case of spontaneous pneumothorax by physical examination and roentgen study is not valid proof that the air escaped from a subpleural air collection instead of via the mediastinum. The evidence of mediastinal air may be transient or unrecognized. This is particularly true when a pneumothorax is found and regarded as adequate explanation of symptomatology. In either spontaneous pneumothorax or mediastinal emphysema the amount of air present may be too small or localized in such a manner that the diagnosis is not made although the history and course be so characteristic that this diagnosis seems probable. The difficulty of diagnosis is greater in the patient in whom the symptomatology is due to pulmonary interstitial emphysema, which in Macklin's²¹ opinion is the precursor of pneumomediastinum and pneumothorax.

From March 15, 1943 to March 15, 1947 we have seen six students with spontaneous pneumothorax without recognized mediastinal emphysema, seven with pneumomediastinum without recognized pneumothorax, and seven in whom the two conditions were associated. Nine individuals with mediastinal emphysema with or without pneumothorax have been seen between January 1 and March 15, 1947. The university enrollment was approximately 18,000 during this period.

Only the 14 cases with mediastinal emphysema will be presented in the following case summaries:

Case 1. A 21 year old student was admitted to the infirmary March 23, 1943. While he was sitting in class he experienced a sharp pain in the precordium radiating through to his back. This pain was accompanied by mild dyspnea. As this patient had suffered from two previous spontaneous pneumothoraces he felt that he had a recurrence so came to the clinic immediately. During the initial examination he became faint. His skin was cool and moist and his pulse was thready. The only significant finding was a peculiar crepitus synchronous with the heart beat heard only at the pulmonic area at the height of full inspiration when the patient leaned forward. His pain disappeared in a few hours and the crepitus could no longer be demonstrated. No evidence of pneumothorax or pneumomediastinum was evident on fluoroscopic examination or chest roentgenogram. During the three day hospital stay he was afebrile. The sedimentation rate and white blood count were normal. A tuberculin test with 1.0 mg. O.T. remained negative. No electrocardiogram was taken. Subsequently this man was seen with recurrent pneumothoraces until after a total of three on the right and two on the left a bilateral chalk poudrage was done in August 1943. Recently he reported that he has had no further difficulty and considers himself to be in excellent health.

Case 2. On May 22, 1945 a 19 year old man noted the abrupt onset of pain in the substernal area radiating through to the back and occasionally to the left arm. The onset occurred while he was in class. His pain was increased by lying flat, by motion, and by breathing. Almost complete relief was obtained by lying on his right side. In January 1945 he had been hospitalized for a spontaneous right pneumothorax. On physical examination there were the usual signs of a left pneumothorax. Cardiac dullness was obliterated. Heart tones were distant and almost obliterated by loud crunching knocking sounds synchronous with the heart beat. The sounds disappeared if he turned on his right side. These signs of pneumomediastinum persisted for 10

days. Throughout his hospitalization he was afebrile. The white blood count and sedimentation rate were normal. An electrocardiogram showed changes, but these persisted after the mediastinal emphysema had disappeared so were regarded as secondary to his known rheumatic heart disease. His tuberculin test with 1.0 mg. O.T. was again negative. It had been checked during the episode in January 1945.

In April 1946 he was seen again as a patient in Wisconsin General Hospital. In March 1946 he had an acute febrile illness associated with an acute right lower lobe cavity which was proved tuberculous by gastric aspiration cultures. One week before he was admitted to Wisconsin General Hospital he noted a pain quite similar to that of June 1945. With this attack he was aware of "noise" in the substernal area. The findings were the same as observed before except for changes on the right. His tuberculin test was positive at the time. Subsequent to his tuberculin test in June 1945 he had been at home. His father had an acute illness which was diagnosed as pulmonary tuberculosis. In December 1945 after this exposure a chest roentgenogram had been taken and was reported as normal. By March 1946 the acute tuberculous disease with cavitation was evident. The mediastinal emphysema was present for several days after admission. The disappearance of the associated left pneumothorax was uneventful.

Case 3. A 21 year old man was admitted on September 24, 1945. On September 22, 1945 he had a sudden severe "grip-like" pain just to the left of the sternum at the level of the fourth rib. This had occurred when he was studying. The pain radiated through to his spine and was increased by movement or any jarring motion. When climbing the hill to classes he had observed shortness of breath and on one occasion a tingling and numbness in the little and ring fingers of his left hand. He had also been conscious of a "grating" over the precordium on several occasions. Physical examination confirmed the impression of mediastinal emphysema. Loud precordial knocking sounds were audible at times without the aid of a stethoscope. The area of cardiac dullness was replaced by hyperresonance. A stereoroentgenogram of the chest showed a small translucent band along the left upper cardiac border. There was no evidence of pneumothorax. The physical findings of mediastinal air persisted for six days. He was afebrile and showed no abnormalities in the white blood count or sedimentation rate. An electrocardiogram was within normal limits. His tuberculin test was positive. His hospital stay was eight days.

Case 4. A 22 year old student was seen on June 24, 1946 with a chief complaint of pain "around his heart" which had started five days before but had increased markedly in severity in the preceding 24 hours. He described the pain as sharp and stabbing in nature and non-radiating. Seven years before he had a questionable history of rheumatic fever. The patient was obviously in pain; his skin was cool and moist. Cardiac dullness was replaced by hyperresonance, and the characteristic crunching sounds synchronous with the heart beat were easily demonstrated and were loudest with the patient in a left lateral position. During his hospitalization from June 24, 1946 to June 30, 1946 he was afebrile. A stereoroentgenogram of the chest was normal as were the sedimentation rate and blood count. Electrocardiograms taken in varying positions showed no significant deviations. By June 29, 1946 the signs of mediastinal air had disappeared. There had been a change from the characteristic knocking crunching sounds to those identical with a pericardial friction rub. A tuberculin test done a short time before was negative with 1.0 mg. O.T. and was not repeated.

Case 5. The first woman with mediastinal emphysema was seen on August 23, 1946. This 26 year old student complained of pain in her left chest and midsternal region. Radiation into the neck and left upper arm had been noted. She was aware of a "sensation of rumbling" in her chest. One or two very similar episodes had been experienced previously, but she had not obtained medical attention. The physical signs typical of mediastinal emphysema were demonstrated; i.e., the loss of normal

cardiac area of dullness and the crunching grating sounds synchronous with the cardiac impulse. On roentgenogram a small left pneumothorax was demonstrated. The electrocardiogram and blood count were normal. A tuberculin test with 1.0 mg. O.T. was negative. During her infirmary stay of three days she was afebrile and after a few hours became symptom free.

Case 6. A 26 year old veteran was seen on January 2, 1947. A sudden precordial pain radiating to his left shoulder had its onset while he was in class. Only a mild dyspnea was admitted. He volunteered that he had experienced several previous episodes of similar nature and although some were more painful than this one he had never been seen by a physician. Subsequent to his infirmary admission he was aware of a peculiar crunching sound in his chest. The physical signs were those of mediastinal air and a small left pneumothorax. However, the typical crunching sounds were more difficult to demonstrate than in several of the previous cases and were heard only on deep inspiration. He had no fever, leukocytosis or increased sedimentation rate. A tuberculin test with 1.0 mg. O.T. was negative. An electrocardiogram was not remarkable. On fluoroscopic examination a small left pneumothorax was seen but no clear cut evidence of mediastinal air. After about 24 hours of infirmary stay his symptoms disappeared and he was discharged on January 6, 1947 to be followed in the clinic. When seen on January 8, 1947 he had remained symptom free but a rubbing sound similar to a pericardial friction rub could be demonstrated at the height of inspiration. On January 13, 1947 the signs of mediastinal air had disappeared. Only a very small left apical pneumothorax remained by fluoroscopic examination.

Case 7. On January 6, 1947 a 21 year old student was admitted with a chief complaint of a sharp pain in his left chest and shoulder. This had its onset suddenly a few hours before and was not preceded by unusual activity. Any motion or respiratory effort increased the pain. When he was first examined the characteristic sounds could not be demonstrated but after several examinations a clicking sound synchronous with the heart beat was heard over the second and third interspaces at the left sternal border. No physical signs of the small left pneumothorax demonstrated by roentgenogram were noted. During his five day hospital stay he remained afebrile and had no leukocytosis. An electrocardiogram was normal. A 1.0 mg. O.T. skin test showed no reaction. After two days he became almost symptom free and was discharged on January 11, 1947. When seen in the clinic on January 13, 1947 he had only occasional discomfort on change of position. The signs of pneumomediastinum could still be demonstrated. A very small left pneumothorax persisted over the apical summit. He failed to keep subsequent appointments but when seen recently he stated he had no further difficulty.

Case 8. The second woman in the group was admitted to the infirmary on the same day as the previous case. On January 4, 1947 while in bed she had sudden pain in the right lower sternal area and was aware of her heart pounding. The pain increased in severity and became quite intense if she lay on her back or took a deep breath. The physical examination was difficult to evaluate because of a severe chest deformity secondary to a dorsal kyphoscoliosis. An extremely coarse friction rub was audible and palpable along the right upper sternal border. After careful examination rubbing sounds synchronous with the heart beat were heard over the pulmonic area. As would be expected the chest roentgenograms in postero-anterior and right lateral position were very difficult to interpret. We could demonstrate no pneumothorax or mediastinal air. What could be visualized of the pulmonary parenchyma appeared normal. Because of the chest deformity and cardiac displacement we did not request an electrocardiogram. She had no fever or leukocytosis. Her pain decreased rapidly and she was discharged symptom free on January 8, 1947. When seen in the clinic on January 10, 1947 she stated she had no recurrence of pain

and no abnormal sounds were heard on examination. A tuberculin test on her routine admission study was positive and was not repeated.

Case 9. On January 23, 1947 a 22 year old student was seen in the clinic. During the war he had been pilot of a navy dive bomber and in August 1945 while aboard ship returning home he had a right spontaneous pneumothorax and had been hospitalized for three months and "nothing else found." Since that time he had frequent right chest pain. During the Christmas holidays in 1946 he again had right sided chest pain and was very short of breath. He consulted his local physician who told him he "had all the symptoms of tuberculosis." The patient was reluctant to accept this diagnosis because he knew his tuberculin test was negative when he entered school in March 1946 and he had a normal chest roentgenogram in October 1946. He recovered sufficiently to return to school and continued to improve until three or four days before he reported for examination. At that time he had more pain in the right chest. Examination showed a right pneumothorax which was confirmed by fluoroscopic examination. No mediastinal emphysema could be demonstrated by physical signs. He refused infirmary care but returned for observation on January 25, 1947. On this date he agreed to enter the hospital because of the finding of increased pneumothorax. Typical crunching sounds were demonstrated at the base of the heart on held inspiration. On January 26, 1947, 600 c.c. of air were removed from the right pleural space, an initial pressure reading of -6 and -8 cm. of water was obtained. No final pressure determination could be obtained, apparently due to expansion of the lung over the tip of the aspirating needle. The patient remained afebrile. The white blood count and electrocardiogram were normal. His tuberculin test with 1.0 mg. O.T. remained negative. Expansion of the lung was progressive without further aspirations. On January 29, 1947 he was discharged essentially asymptomatic. When seen in the clinic on January 31, 1947 a small right pneumothorax persisted and rubbing sounds identical with those of a pericardial rub were heard. Due to a misunderstanding in instructions he did not return until February 10, 1947. He again had chest pain but this was pleural in character and was over the lower lateral chest wall. No signs of pleural friction rub could be demonstrated, nor could any signs of mediastinal air be found. On fluoroscopic examination the right pneumothorax had disappeared and only a slight pleural reaction at the right sulcus remained. A few days later he reported that the chest pain had completely disappeared.

Case 10. A 34 year old graduate student was admitted on February 15, 1947. On February 14, 1947 while eating breakfast he noted the onset of pain over the left chest anteriorly and over the precordium. His pain was increased on motion and deep breathing. On moderate exercise a mild dyspnea had been present. The physical findings were those of a left pneumothorax and mediastinal emphysema. As noted in the previous cases the precordial area was hyperresonant and the usual knocking crunching sounds were heard over the entire precordium. Fluoroscopic examination on February 15, 1947 revealed almost complete collapse of the left lower lobe, but the lobe was aerated. The upper lobe was not collapsed. There was a large pocket of air between the upper lobe and the heart shadow. Whether this was in the mediastinal tissues or a pneumothorax pocketing could not be determined. By the morning of February 16, 1947 the pneumothorax had increased so that both lobes were collapsed to small airless "nubbins." In spite of this increased pneumothorax the patient was much more comfortable. Mediastinal air was present to physical examination.

On February 17, 1947, 1000 c.c. of air were removed from the left pleural space. The initial pressure was atmospheric and the final reading was -1 to -3 . On fluoroscopic examination the next morning there had been no appreciable decrease in pneumothorax so 1,400 c.c. of air were removed with final pressure readings of -16 to -20 . An immediate fluoroscopy showed some mediastinal shift to the left. The left upper lobe had not become air containing although only about 15 per cent

pneumothorax persisted. On February 19, 1947 aeration of both lobes was complete and there remained only about 10 per cent residual pneumothorax. An electrocardiogram was normal. Tuberculin tests with .01 and 1.0 mg. O.T. were negative. There was no significant leukocytosis.

On February 22, 1947 he was seen as an outpatient and reported that he still had some pain but felt quite well. Signs of pneumomediastinum persisted and there was evidence of this air on a single chest roentgen-ray in a small translucent zone along the left cardiac border. There remained a small left pneumothorax.

On February 25, 1947 the signs of mediastinal air had disappeared. By February 28, 1947 there was no evidence of mediastinal or pleural air on fluoroscopy. He felt entirely well and had returned to classes although he was still cautious about overexertion.

It is interesting to note that a roentgenogram taken March 17, 1943 showed evidence of small emphysematous blebs at both apices. There had been no significant change on the right side, and on the left side comparison of densities was difficult due to pneumothorax.

Case 11. On February 24, 1947 a 26 year old student was examined in the clinic. On February 5, 1947 while in bed he experienced a sudden pain in the lower anterior left chest. At this time he stated he had just recovered from a rather severe "cold" which had been accompanied by a cough. The pain was increased by deep breathing and was accompanied at times by a sound "like tissue paper crackling" over the lower sternal area. He was seen by a local physician who taped his left chest for "pleurisy." However, the patient experienced no relief from this and because of continued pain he reported to the student clinic and a chest roentgenogram was secured on February 19, 1947. This showed a small left pneumothorax. Because of our interest he was checked for mediastinal emphysema on February 24, 1947. At this time no physical sign of the left pneumothorax could be demonstrated. There was loss of cardiac dullness. His precordium was hyperresonant. A typical crunching sound of pneumomediastinum was present. Because of his relative freedom from symptoms and the long continued course with some improvement he was very reluctant to enter the hospital so he was seen again on February 26, 1947 in the clinic. At this time he was feeling better. The signs of mediastinal air persisted. When seen on February 28, 1947 the pain had increased and there was evidence of mediastinal air on fluoroscopic examination with the patient in the left anterior oblique position. At this time he was convinced that hospital care was desirable. On March 1, 1947 at 8 p.m. he had a sudden sharp pain in the epigastrium and in the right lower quadrant. He also noted some pain referred to the left trapezius at this time. Examination showed generalized abdominal tenderness with some rebound tenderness. He had no febrile response to this. By the next morning he was free of pain and had no significant physical finding. Fluoroscopic examination revealed no air under the diaphragm and no recurrence of the left pneumothorax.

On March 3, 1947 he developed a very harassing cough accompanied by a low grade fever. This was entirely similar to the tracheobronchitis which was prevalent in the student body. He had been in the same room with Case 12 until that patient had been recognized as having tracheobronchitis. With the use of steam inhalations and codein his cough was fairly well controlled and gradually disappeared. He continued to have physical signs of mediastinal emphysema until March 6, 1947. All his symptoms disappeared and he was discharged on March 11, 1947. His sedimentation rate and leukocyte count were normal. A tuberculin test with 1.0 mg. O.T. was negative. An electrocardiogram showed no significant deviations.

Case 12. A 24 year old man was admitted to the infirmary on February 28, 1947. His chief complaint was substernal pain. He stated that he had noted several transitory attacks of substernal pain during the past month. A more severe episode oc-

curred at 4:30 p.m. on February 27, 1947 and lasted about five minutes. The pain radiated directly through to his back. The morning of February 28, 1947 a hacking cough developed. He had no shortness of breath. On physical examination there was no evidence of pneumothorax. There was hyperresonance over the precordium. Typical knocking rustling sounds synchronous with the heart beat were heard over the lower sternal area and were loudest with complete expiration. During the evening of February 28, 1947 his temperature rose to 104° F. and his cough became very annoying. On March 1, 1947 the signs were essentially unchanged. His fever subsided promptly as did the cough. On March 4, 1947 his symptoms and signs had disappeared completely and he was discharged. An electrocardiogram was normal except for tendency to right axis deviation. His total leukocyte count was 8450 and 81 per cent polymorphonuclears were present. A tuberculin test done previously was positive and was not repeated. His chest roentgenogram showed no evidence of pneumothorax or mediastinal air and was unchanged from previous roentgen-rays in 1942.

Case 13. A 29 year old woman was admitted to the hospital on March 3, 1947. Her complaint was a "tight feeling in the chest." For three weeks she had noted episodes of substernal discomfort "like a hand gripping her." On the afternoon of admission while in class she had a more severe attack. She complained of feeling faint when first seen. She had observed that the pain was increased markedly by change in position. On physical examination her skin was cold and clammy and the fingernails were subcyanotic. Pulse rate was 80 per minute, blood pressure 132/82. The area of cardiac dullness was replaced by a hyperresonance. The characteristic crunching sounds were not demonstrated until the following day when they were heard clearly at the left third interspace at the sternal border. These sounds persisted but diminished greatly until March 6, 1947 when they were no longer audible, and she was discharged. On March 8, 1947 when she returned to the clinic she still had very slight precordial pain. There were no signs of mediastinal emphysema or pneumothorax by physical examination or fluoroscopic examination. Her tuberculin test remained negative. The blood count was normal. No electrocardiogram was taken. A chest roentgenogram during her infirmity stay showed no abnormalities.

Case 14. A 19 year old student was admitted on March 10, 1947 with a chief complaint of chest pain. Two days before she noted an abrupt onset of mild pain in the left anterior chest which became worse progressively. Her pain was accentuated by coughing, any motion and especially by movement of her left arm. She complained of severe pain over the fourth costochondral area when she moved her left arm or on pressure over this area. When first seen in the clinic the characteristic sounds of mediastinal emphysema were not heard. Because of a history of having been in a "scuffle" shortly before the onset of the pain the diagnosis of a rib fracture was considered, but there was no evidence of any fracture by roentgenogram. After being admitted to the infirmity the usual signs of mediastinal emphysema were elicited. The precordium was hyperresonant and loud crunching sounds were audible over the heart and synchronous with the heart beat. The hyperesthesia in the fourth costochondral area persisted about two days. On admission she had a fever as high as 101° F. and the following day the maximum fever was 101.8° F. She complained of some generalized malaise and mild sore throat. Her leukocyte count was normal. A tuberculin test had been positive previously and was not repeated. On chest roentgenogram there was no evidence of pneumomediastinum or pneumothorax. An electrocardiogram was normal. After March 11, 1947 she remained afebrile and her symptoms rapidly disappeared. On March 14, 1947 only an occasional rubbing sound was heard over the pulmonic area. As she was asymptomatic she was discharged to continue observation in the clinic. When seen on March 22, 1947 she was entirely symptom free and no evidence of pneumomediastinum could be demonstrated.

DISCUSSION

During the past four years we have seen a total of 20 students with spontaneous pneumothorax, mediastinal emphysema or a combination of these two conditions.* In this same interval we have seen several other individuals in whom the diagnosis was considered because of the history and course, but in whom diagnostic physical signs could not be demonstrated nor could air in the mediastinal structure or along the pulmonary vessels be demonstrated by roentgenogram. However, in several of these individuals there was hyperresonance over the precordium and a peculiar crepitus synchronous with respiration but not with the heart beat.

The history of mediastinal emphysema is quite characteristic. The pain is rather sudden in onset and may vary a great deal in severity. The most common location of the pain is substernal with frequent radiation straight through to the back or into the left neck or shoulder. Occasionally the pain may radiate in the manner of angina pectoris into the little and ring fingers of the left hand. The association of pain with change in position or with any jarring motion is noteworthy. Six of the 14 patients with mediastinal emphysema were aware of peculiar sounds over the precordium.

The physical signs are distinctive. The most characteristic is the crunching sound synchronous with the heart beat. This may vary greatly during the episode and with change in position or phase of respiration. The intensity of the sounds bears no relationship to the severity of the patient's symptoms; often the patient is almost free of pain when the crunching is most pronounced. Frequently the sound may be identical to that heard in pericardial friction rub. This type was heard almost routinely after the loud crunching sounds had disappeared. In Case 8 a loud pleural friction rub was heard along the right sternal border in addition to the rubbing sounds synchronous with the heart beat. In our series hyperresonance over the precordium was a constant finding. None of the group showed any physical evidence of subcutaneous air. In only one individual was retroperitoneal air dissection suspected.

We were able to demonstrate mediastinal air by roentgenogram or fluoroscopic examination in only three of the 14, although repeated examinations were done in various positions. Likewise we found no subcutaneous air in the neck or elsewhere. Air in the mediastinum is difficult to visualize unless it is localized or relatively large in amount. This circumstance would be anticipated due to lack of contrast because of the air containing structures surrounding the mediastinum. The presence of an associated pneumothorax increases this difficulty.

Although electrocardiograms were obtained in the majority of the group and taken in varying positions we were unable to demonstrate any character-

* Since this paper was submitted the author has seen seven students with spontaneous pneumothorax. These pneumothoraces all occurred on the right. In six of the seven there was an associated mediastinal emphysema.

istic pattern for mediastinal emphysema with or without pneumothorax. The value of the electrocardiogram, as has been pointed out previously, lies in the exclusion of the more serious conditions which might be confused with this symptom complex; i.e., coronary occlusion and pericarditis.

In this series the pain and symptoms were not of the severity to be confused readily with coronary occlusion or pericarditis. In both the groups with spontaneous pneumothorax and mediastinal emphysema the diagnosis might have been overlooked or attributed to muscle strain, neuritis, cardio-spasm, pleuritis or so-called "witch's stab."

Likewise we found these individuals to have no significant change in the leukocyte count or sedimentation rate. The three patients who demonstrated a febrile response (Cases 11, 12 and 14) were diagnosed as having an unrelated tracheobronchitis. In these patients the symptoms of mediastinal emphysema preceded the onset of the acute tracheobronchitis. All were seen at the time when the incidence of this infection, probably virus in type, was prevalent in the entire student body. Although we used no chemotherapy or antibiotics, no complications developed as the result of this superimposed disease. Their courses were entirely comparable to those patients having similar infection without mediastinal emphysema. In spite of the difficulty in controlling the cough accompanying the tracheobronchitis, none of these individuals had evidence of any marked increase of mediastinal emphysema by signs or symptoms. The duration of symptoms varied widely. Several of the cases from the history had continued air leaks or repeated episodes of alveolar rupture. The evidence of mediastinal emphysema to physical examination may be extremely transient as noted in Case 1.

Recurrences of mediastinal emphysema have been pointed out by Schwartz, McIlroy and Warren,⁹ and by Schendstok.¹¹ In Case 2 there was a verified recurrence of mediastinal emphysema and left pneumothorax as well as one previous episode of right pneumothorax. In Cases 1 and 9 there had been previous episodes of pneumothorax verified by roentgen study. In Cases 5 and 6 the history was very suggestive of previous pneumothorax and/or mediastinal emphysema. Of the group with pneumothorax without recognized mediastinal emphysema one of the six had a history of very probable pneumothorax and two had observed recurrences, one within two weeks after expansion and the other the following year. The majority of the entire group is too recent to evaluate from the standpoint of recurrences.

As observed in previous reports there is a high incidence of associated pneumothorax. Of the 14 with mediastinal emphysema seven had pneumothorax, six on the left and one on the right. The reason for the predominance of left pneumothorax is unexplained although to our knowledge only one case of right pneumothorax associated with pneumomediastinum has been recorded.⁹ The amount of pneumothorax is not constant but is not necessarily small as evidenced by Cases 9 and 10. In our experience the occurrence of pneumothorax does not alter the course of a mediastinal emphysema. The appearance of recognized mediastinal emphysema in Case 9 was in the

face of an increasing pneumothorax. In Case 11 the mediastinal emphysema increased after the pneumothorax had disappeared and although a very probable episode of retroperitoneal air dissection occurred there was no recurrence of the left pneumothorax.

Tuberculin testing was done on the entire group except those who were known to be tuberculin positive from their student health records. Of the 20 students only four were tuberculin positive and these were all tuberculin positive at the time of their routine admission tuberculin tests. This percentage is essentially the same as in the entire student body. None of the individuals showed any lesions regarded as tuberculous in nature. The presence of pleural adhesions with pneumothorax was not regarded as tuberculous in origin and was seen only in two individuals who were tuberculin negative. Of the entire group only one student, Case 10, had roentgen evidence of emphysematous blebs. The student with the severe chest deformity may well have areas of unrecognized pulmonary emphysema due to overdistention of portions of the lung.

Of the entire series males have outnumbered females 14 to 6. This is not a disproportionate number of males considering the sex-ratio in the University population.

Treatment of spontaneous pneumothorax in this series has been symptomatic. It has been our policy to hospitalize the individuals if they are seen shortly after the onset or if they are having acute pain or other symptoms. With the spontaneous pneumothoraces which are small and relatively symptom free when they first present themselves for examination several days after the onset, we have observed them frequently as outpatients to check the progress of expansion. This policy has been adopted from previous experience in the Student Health Service and from other patients who are not included in this study. Normal respiratory effort does not increase the intrabronchial pressure and therefore should not serve to continue the leak through the alveolar rupture. The patients are cautioned against the possible ill effect of any effort with a closed glottis, such as lifting, coughing, etc. Aspirations of pleural air were done to relieve dyspnea, or if the pneumothorax was large and asymptomatic, to hasten reexpansion. If the pulmonary parenchyma is normal, the bronchial tree patent and pleura normal, it is impossible to create any significantly negative intrapleural pressure with ordinary aspirations.²³ Therefore, we see no reason to fear that aspiration is going to reopen any rupture of alveolar wall. If, as occasionally occurs, the lung or portions of the lung are atelectatic, as in Case 10, we believe that aspiration is indicated to allow prompt reaeration of the lung before infection or other complications of bronchial occlusion occur. If a persistent leak is present it may be recognized by failure of change of manometric readings or failure of expansion following aspiration of air. The treatment of the rare case in whom there is persistent or frequently recurrent pneumothorax is not within the scope of this report.

The benign course of the average spontaneous pneumothorax and our earlier experience with mediastinal emphysema have encouraged us to treat these individuals in a similar manner. If their symptoms are acute and the onset recent with increasing symptoms, we hospitalize them promptly for symptomatic treatment and relief of pain. At the same time close medical attention is available if the rare complication of serious interference with venous return or bilateral pneumothorax should occur. As soon as the patient is symptom free and the signs of mediastinal air are decreasing he is discharged to be followed as an outpatient. As the majority of cases show no correlation between the onset of symptoms and physical exertion, the probability of preventing recurrence by continued bed rest seems unlikely. Recurrences or sudden increase in symptoms have been reported in patients who are at bed rest.^{9, 11}

These individuals must be reassured that they have no serious pulmonary or cardiac pathology. The rather dramatic onset with occasional severe pain is alarming to the individual. This psychic trauma plus continued bed rest for periods of weeks will serve to convince a fair number of patients that they have serious pulmonary or cardiac disease and they will become cardiac or pulmonary invalids. The problem of recurrent episodes must be admitted but not stressed.

The use of sulfonamides or antibiotics as a prophylaxis against mediastinitis is not recommended. They should be reserved for concurrent or complicating infections. Cough should be controlled to prevent the marked increase in intrabronchial pressure.

CONCLUSIONS

1. Twenty cases of spontaneous pneumothorax and pneumomediastinum were observed in a four year period. There were six cases of pneumothorax without recognized mediastinal air, seven individuals with mediastinal emphysema without recognized pneumothorax and seven patients with a combination of the two conditions.

2. In this series there was no significant variation in the incidence among males and females considering the disproportion among the university population.

3. Short periods of symptomatic treatment with early ambulatory observation have been entirely satisfactory in our experience.

4. There have been no complications in 14 cases of spontaneous mediastinal emphysema.

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HYPERTENSIVE CEREBRAL SWELLING, A CHARACTERISTIC CLINICO-PATHOLOGIC SYNDROME *

By I. MARK SCHEINKER, M.D., *Cincinnati, Ohio*

THIS presentation aims to analyze the brain findings of only such cases of hypertensive brain disease as are characterized by a sudden onset and rapid progression of the following clinical symptoms and signs: Severe headache, drowsiness, confusion, restlessness and delirium accompanied by signs of increased intracranial pressure, such as elevation of spinal fluid pressure and bilateral papilledema; and occasionally by convulsions, impairment of vision and weakness of extremities. This acute clinical syndrome may last for days and then completely remit, or it may in some instances be the cause of rapid death.

Before the pathologic findings characteristic of this condition are presented in detail, it would seem appropriate to review the cerebral lesions pathognomonic for hypertensive brain disease in general.

In previous contributions^{1,2} attention was called to vascular alterations in hypertensive encephalopathy. The histologic changes which were regarded as typical consisted of hyaline degeneration and fibrotic thickening of the vessel wall with narrowing or complete obliteration of the vascular lumina. It has been emphasized that these vascular changes confined to arterioles and capillaries are different from those found in arteriosclerosis and are to be interpreted as a special form of hypertensive arteriolopathy. The alterations of the nervous parenchyma characterized by diffusely scattered small foci of old and recent softening were interpreted as secondary to the vascular lesions.

In addition to the arteriolar changes two types of *venous* alterations were recently described^{3,4}: (a) Reversible changes characterized by stasis, congestion and distention of the vascular lumina; (b) structural lesions of the vessel wall manifested by advanced signs of degeneration, necrosis and/or an extreme degree of atrophy.

Whereas the arteriolar changes were interpreted as significant for the diffuse focal areas of softening and gliosis of the nervous parenchyma typical of hypertensive encephalopathy, the alterations of the cerebral veins were regarded as responsible for the origin and pathogenesis of massive intracerebral hemorrhages so often encountered during the terminal phase of hypertensive brain disease.

The present investigation is based upon 12 cases that have been subjected to histopathologic study. No attempt will be made to describe the

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From the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine, Cincinnati, Ohio.

findings in each case. Two illustrative cases, however, are presented here-with in detail.

CASE REPORTS

Case 1. A 34 year old colored male was known to have had high blood pressure for a period of more than one year. He was apparently well until four months prior to his admission to the hospital, at which time he began to have brief spells of visual difficulty in which he said he couldn't see. In addition he complained of shortness of breath on exertion and occasional swelling of the feet. For the 10 days preceding admission the patient had complained of severe occipital and frontal headaches. An hour and a half before his admission he became confused, delirious and, according to the information given by his wife, "had talked out of his head."

On admission the patient was semi-stuporous; he responded only occasionally to simple commands.

There was a fine horizontal nystagmus; the eyes were deviated toward the right. The optic discs were clearly outlined; there were extreme narrowing of the arteries and pronounced fullness of the veins. Fresh hemorrhages were seen in the right retina.

Resistance of the limbs to passive movement was reduced. On the evening of admission the patient was thought to have a left hemiparesis; on painful stimuli he moved the right lower extremity slightly better than the left. The abdominal reflexes were absent. There was a right Hoffman response. Pyramidal signs were equivocal on both sides.

The heart was enlarged to the left and the apex beat was forceful. There was a harsh systolic murmur to the left of the sternum at the second interspace and in the pulmonic area. There was mild edema of the ankles. Respiration was fast and noisy.

Clinical Course: The patient remained stuporous; the edema increased and spread to involve the trunk and face. The patient died 66 hours after his admission to the hospital.

Laboratory Data: The systolic blood pressure ranged between 240 and 280 mm. of mercury (on occasion, beyond the range of the manometer), the diastolic between 120 and 150. The blood analysis was as follows: hemoglobin 11 grams, red blood count 3.8 million per cubic millimeter, white blood count 19,500 per cubic millimeter, the blood urea nitrogen 100 mg. per 100 c.c., blood Kahn negative. One urinalysis showed a specific gravity of 1.010 and a three plus albumin test. There were 70 to 80 white blood cells and 4 to 5 red blood cells per high power field with a few epithelial cells in the smear.

A lumbar puncture revealed an initial pressure of 385 mm. of water. After the removal of 6 c.c. of fluid resembling water, the final pressure was 190 mm. There were four white blood cells and 12 red blood cells per cu. mm. The protein was 130 mg. per 100 c.c., and the Wassermann reaction was negative. There was a first zone gold curve (4442210000).

Pathologic Findings: The extraneural findings were chronic pyelonephritis, nephrosclerosis, hypertrophy and dilatation of the heart, and generalized arteriosclerosis.

On gross examination of the brain the gyri were flattened and broadened, the sulci narrowed. There was an old area of softening about the posterior portion of the left Sylvian fissure. There was a well-defined cerebellar pressure cone. Although the temporal lobes appeared generally swollen, there was no uncus herniation. There was sclerosis of the vessels of the circle of Willis.

Coronal sections through both hemispheres revealed broadening of the white matter, compression and narrowing of the cortical gray matter and almost complete obliteration of the lateral ventricles (figure 1). There was a small area of recent

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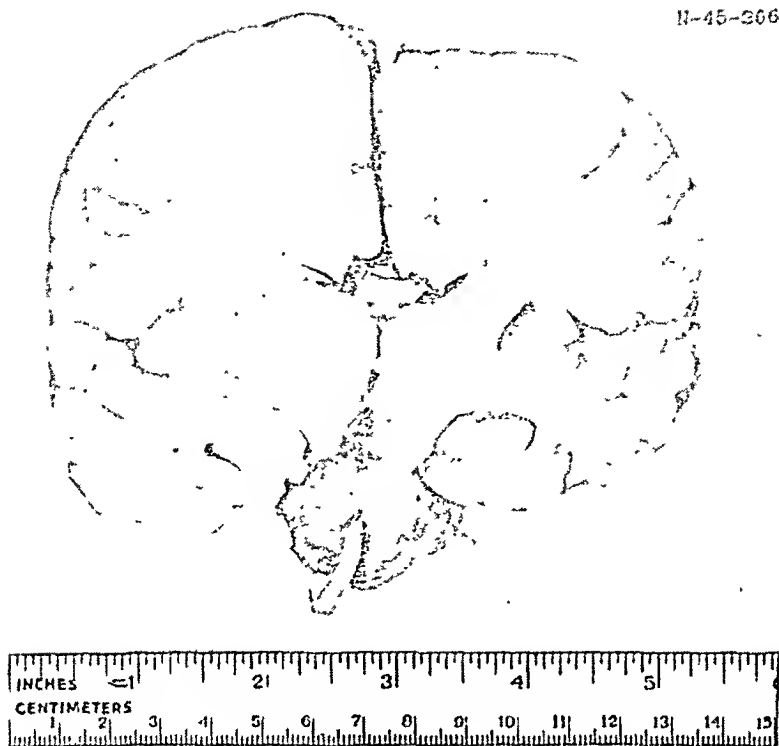


FIG. 1. *Case 1.* Diffuse swelling of the white matter of both hemispheres. Note the compression and narrowing of the cortical gray matter and the obliteration of the lateral ventricles. (The corpus callosum was severed at autopsy to allow for better penetration of the formalin solution.)

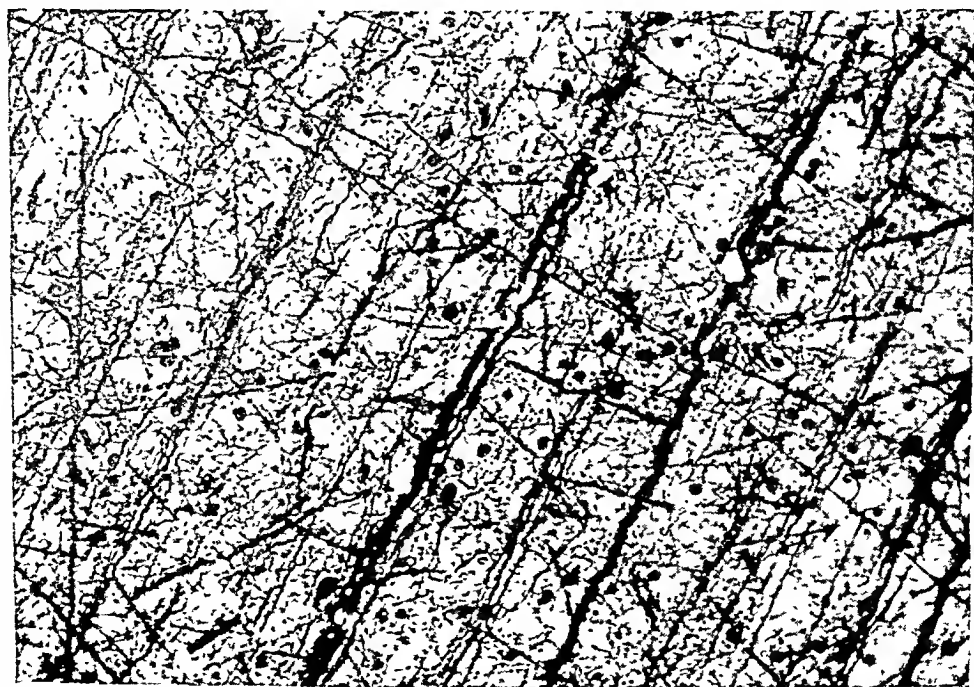


FIG. 2. *Case 1.* Irregular swelling and partial destruction of the nerve fibers of the white matter. Bodian silver impregnation; $\times 220$.

softening transecting the left internal capsule near the head of the caudate nucleus. In the white matter of the left occipital lobe there was a ball hemorrhage measuring 8 mm. in diameter. The scar of an old softening in the right hippocampus was observed; and also an old cyst 1 cm. in length involving the lateral portion of the left internal capsule and the mesial portion of the globus pallidus.

The microscopic examination disclosed tremendous swelling of all the constituents of the nervous parenchyma. These changes hardly would have been seen in preparations stained with hematoxylin and eosin; stained by the Bodian and Loyez methods the characteristic findings of brain swelling were obvious (figure 2). The majority of the nerve fibers and myelin sheaths were irregularly swollen; numerous fusiform varicosities were found throughout their course. The glia did not escape the process of swelling. In all sections taken from the white matter there was rarefaction of the tissue. The subeortical U-fibers were relatively well preserved. The cortical ribbon was compressed, but otherwise was normal.

There were two principal types of vascular abnormalities: arteriolar hyalinization characteristic of hypertensive arteriolopathy, and congestion and stasis of veins associated with degeneration and atrophy of their walls.

Case 2. A 38 year old colored male was perfectly well until four weeks before admission to the hospital, when his vision began to fail. Recently he had noticed bloody urine. No cardiac symptoms were present.

On examination papilledema associated with hypertensive neuro-retinopathy was found. The heart was enlarged to the right. The blood pressure was 244/156.

The Wassermann reaction in blood was negative; blood urea nitrogen at the time of the admission was 26 mg. per 100 c.c.; a few days before death blood urea nitrogen was 60 mg. per 100 c.c.

He grew steadily worse; four weeks after his admission he became lethargic and developed right hemiparesis. Coma deepened and death occurred the following day.

The gross pathologic abnormalities at autopsy were pulmonary congestion and edema, malignant nephrosclerosis, marked hypertrophy and dilatation of the left ventricle of the heart.

Gross Description of the Brain: The brain appeared markedly swollen, the gyri were extremely flattened, the sulci narrowed or completely obliterated. The leptomeninges overlying the surface of the brain were slightly thickened. On the under surface of the brain there was to be seen an uncus herniation measuring 3 mm. in width. There was an obvious cerebellar pressure cone, particularly marked on the left. The lumina of the larger blood vessels at the base were dilated; the vessel walls were thickened and harbored a few sclerotic plaques. Coronal sections disclosed a far advanced degree of swelling of both cerebral hemispheres (figure 3). In addition, there was found in the left putamen a hemorrhagic area measuring 1.5 cm. in diameter. An old area of softening, bounded by a yellowish brown discoloration, was present in the left thalamus.

Microscopic Findings: Sections were taken from the cortex of the parietal, frontal and occipital lobes, basal ganglia, hypothalamus, cerebellum and pons, and were stained with hematoxylin and eosin, hematoxylin and van Gieson, and cresyl violet; the Loyez and Bodian methods were also employed.

The histologic examination revealed two principal types of abnormalities: (1) changes of the brain parenchyma and (2) vascular alterations.

The main histologic alterations, involving large areas of the white matter of both hemispheres, consisted of acute swelling of all constituents of the nervous parenchyma. A striking manifestation of the process was best seen in sections stained by the Bodian silver impregnation method (figure 4). Most nerve fibers were considerably swollen, intensely stained and irregularly outlined. Some of the axons disclosed advanced degenerative lesions characterized by fragmentation; occasionally they were broken

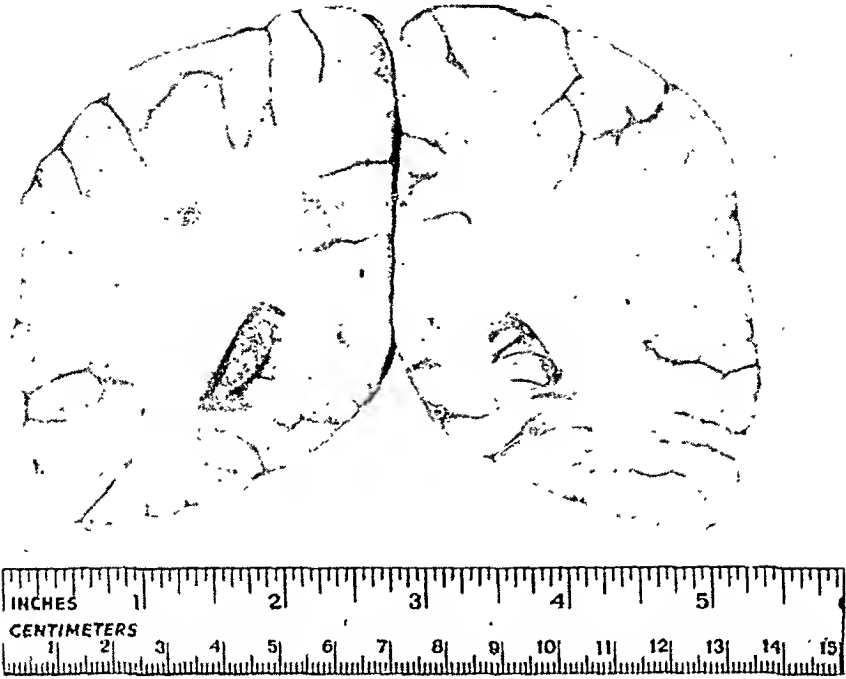


FIG. 3. *Case 2.* Diffuse swelling of the white matter of both hemispheres. Note the "ball hemorrhage" on the right.

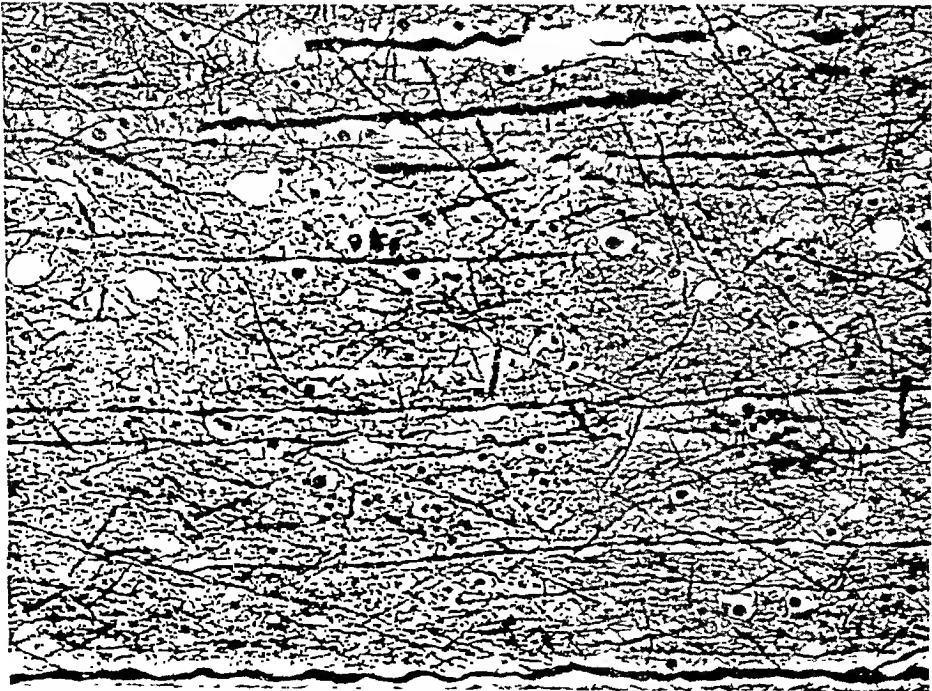


FIG. 4. *Case 2.* Considerable swelling and irregular outline of the nerve fibers of the white matter. Note the swollen oligodendroglia cells. Bodian silver impregnation; $\times 220$.

into granular debris or were undergoing fragmentation. In addition there was to be seen a diffuse swelling of the oligodendroglia cells. Loyez preparations revealed diffuse and extensive swelling and irregular beading of the myelin sheaths. These changes were most prominent in the white substance. Many of the myelin sheaths were broken up into globules.

There was tremendous distention of the perivascular spaces (figure 5) which harbored large masses of serous fluid and a few cellular elements, chiefly histiocytes and macrophages.

In all sections structural changes in the blood vessel walls were frequently observed. These consisted of marked thickening, homogenization and hyalinization of the capillaries and arterioles (figure 6). In sections stained with hematoxylin and van Gieson, and by the Bodian silver method, it could be seen that the essential pathologic process was characterized by hyaline degeneration and thickening of the vessel wall. The vessel lumina appeared extremely narrow or completely obliterated. In some of the capillaries and arterioles the entire vessel wall appeared to be transformed into a strand of connective tissue. The mesenchymal fibrils running longitudinally or transversely were devoid of elastin and easily impregnated with the Bodian silver stain, and stained red with the hematoxylin and van Gieson stain. Some of the smaller blood vessels were surrounded by small accumulations of lymphocytes and a few fat granule cells (figure 6). These cells usually were confined to the perivascular space and did not infiltrate the vessel wall.

Summary of Pathologic Findings: The outstanding pathologic brain changes found in all cases consisted in a tremendous degree of cerebral swelling. The gross findings were characterized by a considerable increase in volume of both hemispheres, flattening of the gyri and narrowing or obliteration of the sulci; considerable enlargement of the central and subcortical white matter with consequent narrowing and compression of the cortical gray; loss of demarcation between white and gray matter; decrease in size or complete obliteration of both lateral ventricles.

In addition there were disseminated ball hemorrhages in various regions of the brain tissue. Only occasionally (in two cases out of 12) were there massive hemorrhages.

The microscopic findings were identical with those recently described as characteristic for the early reversible stage of cerebral swelling, designated as cerebral tumefaction.⁵ As already emphasized, microscopic findings characteristic of cerebral tumefaction may easily be overlooked in routine sections stained with hematoxylin and eosin. They are best noted with careful study of silver impregnations, such as Bodian or Bielschowsky methods.

The pertinent histologic findings may be summarized thus: (1) parenchymatous changes with evidence of swelling of the nerve fibers, myelin sheaths, glia and particularly of the oligodendroglia; (2) vascular alterations confined to the small veins and capillaries characterized by (a) congestion and stasis, and by (b) swelling and degeneration of the endothelial cells. These changes were predominant in the white matter.

In addition there were arteriolar changes characteristic of hypertensive arteriolopathy.⁴ Only occasionally were there seen small focal areas of softening or glial scarring.

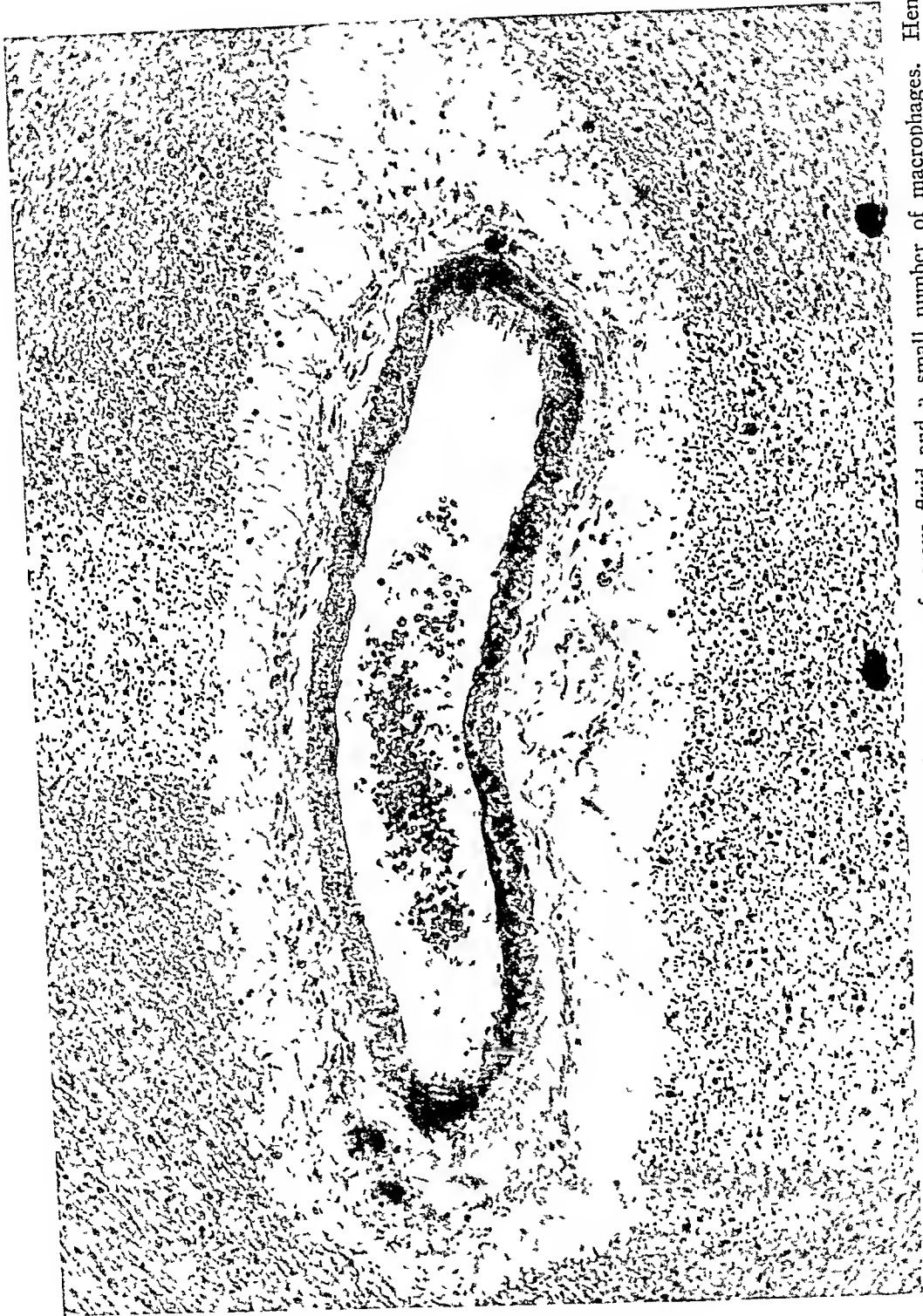


FIG. 5. Case 2. Distended perivascular spaces harboring large masses of serous fluid and a small number of macrophages. Hematoxylin-eosin; $\times 180$.

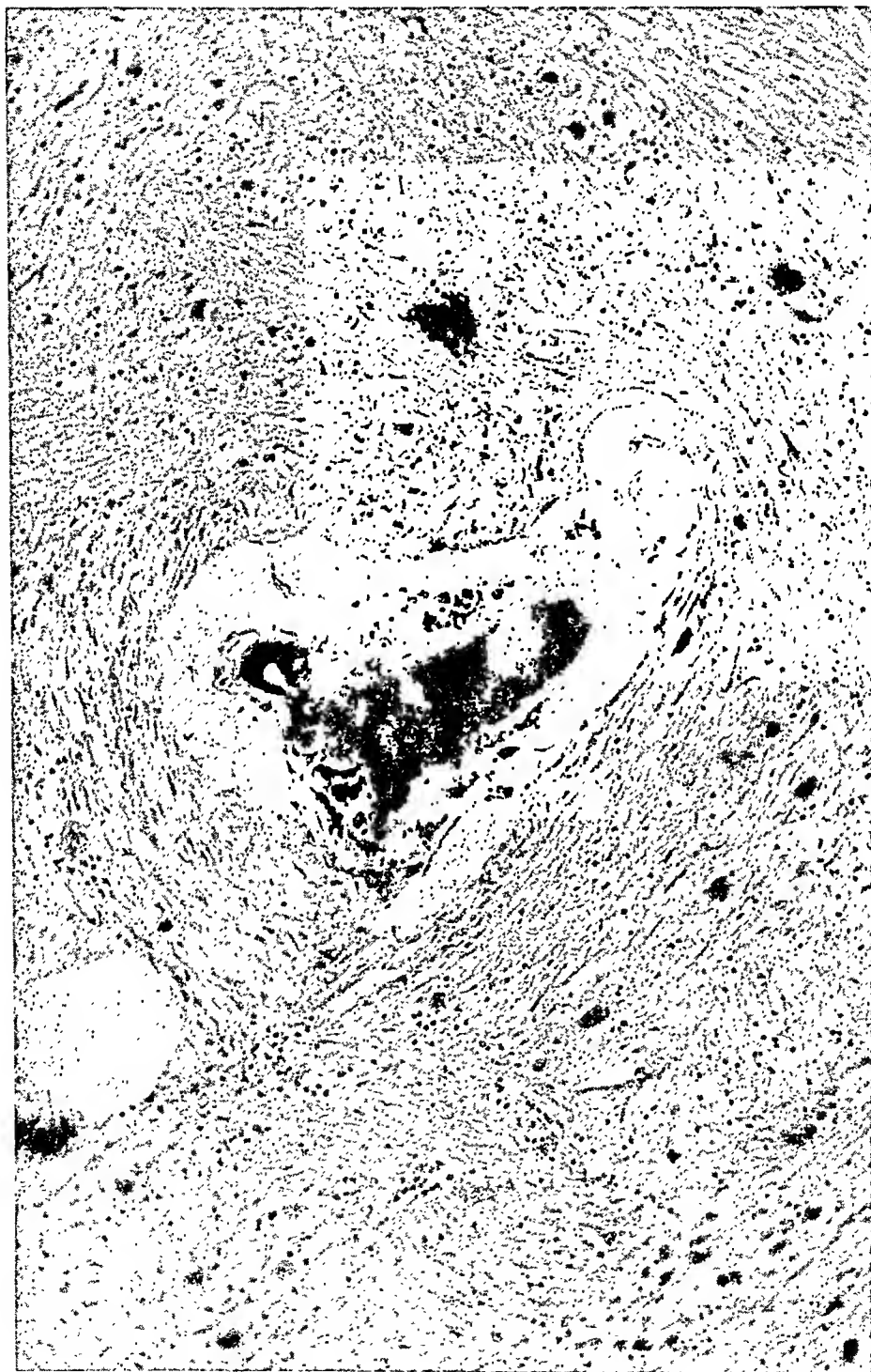


FIG. 6. Case 2. Far advanced form of hypertensive arteriolopathy. Hematoxylin and eosin; $\times 180$.

CLINICOPATHOLOGIC CORRELATIONS

The diffuse swelling of wide areas of cerebral tissue explains why the clinical symptomatology occasionally resembles the acute manifestations of brain tumor. The remarkable parallelism may be attributable to the fact that the clinical syndrome under discussion rests upon the effect of an acute increase in the bulk of the brain with consequent increase in intracranial pressure. The clinical manifestations of papilledema and considerable elevation of the cerebrospinal fluid pressure, noted in almost all cases under observation, corroborate this conclusion.

As already emphasized, the fulminating course and alarming clinical symptoms may occasionally end in rapid recovery with complete disappearance of most of the clinical symptoms. Needless to say, the reversibility of the process is best explained by the relatively mild degree of the pathologic findings characteristic of the early stage of cerebral swelling. Reversible vascular alterations, associated with increased permeability of the vessel wall for serous fluid, have been stressed by the author as the most significant feature in the pathogenesis of cerebral swelling.⁵ The functional vascular alterations are characterized by a complete relaxation of the vessel walls of the smaller veins and capillaries, resulting in enormous distention and stasis. These vascular changes are associated with signs of increased permeability for serous fluid of the vessel walls, thus leading to an increase in intra- and extracellular fluid content of the nervous parenchyma.

The clinical syndrome under discussion previously has been referred to as "vascular crisis" (Pal⁶ and Allbutt⁷), "pseudo-uremia" (Volhard⁸), "hypertensive encephalopathy,"⁹ and, more recently, as "malignant hypertension."¹⁰ Pal and Allbutt offered vascular spasm as an explanation for the pathogenesis of the syndrome. The histologic examination of the brain in our series of cases failed to reveal morphologic evidence of angiospastic phenomena. Venous and capillary distention were the predominant vascular alterations. However, it is possible that the final relaxation of the smaller blood vessels with resultant venous distention may have been preceded by brief angiospastic phenomena which, owing to their transient nature, cannot be detected morphologically.

CLINICAL CONSIDERATIONS

Clinical manifestations referable to nervous system alterations in cases of hypertensive cerebral swelling may be summarized briefly, as follows: Sudden onset of an increasingly severe headache, with rapid development of progressive drowsiness; confusion and delirium, frequently associated with vomiting of projectile character; impairment of vision and generalized convulsions. Bilateral papilledema and marked elevation of the cerebrospinal fluid pressure, which are the most consistently observed findings, are pathognomonic enough to permit clinical recognition of the syndrome. The notable

parallelism between this syndrome and the manifestations of a rapidly expanding space-consuming intracerebral process (malignant neoplasm, cerebral abscess) explains the ease with which the two conditions may be confused. The presence of arterial hypertension, however, in combination with hypertensive retinopathy and with signs and symptoms of hypertensive cardiovascular disease, permits differentiation of hypertensive cerebral swelling from cerebral space-consuming lesions.

In the survey of clinical data of the 12 cases of the present study, particular attention was given to clinical manifestations antecedent to the fatal development of hypertensive cerebral swelling, such as cardiovascular and renal disorders, clinical evidence of uremia, earlier episodes of focal or cerebral involvement and, finally, the character of the cerebrospinal fluid both preceding and during the fatal illness.

Age: The majority of cases of hypertensive cerebral swelling occurred between the ages of 24 and 63. The average age was 46.

Duration of Hypertension: It was not always possible to establish accurately the duration of hypertension. Exploration of various sources for earlier blood pressure measurements yielded the following data: The mean duration of arterial hypertension preceding the fatal illness was 4.1 years. In all cases but one both the systolic and diastolic pressures were extremely high. The systolic ranged between 200 and 270; the diastolic between 150 and 165.

Optic Fundi and Retinal Arterioles: Examination of the optic fundi is of paramount significance for the recognition of hypertensive cerebral swelling. In all but three cases (in one case the examination of the fundi was not made), there were definite signs of papilledema ranging from "blurring" of the disc margins to pronounced swelling of from 3 to 4 diopters.

Examination of the retina disclosed in all cases various stages of hypertensive retinopathy characterized by constriction and thickening of the retinal arterioles, cotton-wool exudate, recent and old hemorrhages and venous congestion.

Spinal Fluid Changes: Strikingly characteristic for hypertensive cerebral swelling is the considerable elevation of the spinal fluid pressure.

In 10 out of the 12 cases, the spinal fluid pressure was high above the norm, ranging between 350 and 470 mm. of water. The other two cases disclosed spinal fluid pressures of 230 and 170 mm. of water.

In eight cases the spinal fluid contained a small number of red blood cells. In two cases there were large numbers of erythrocytes. There was no, or very mild, increase in the number of white blood cells.

In four cases the protein was above 130 mg. per 100 c.c. In the remaining cases, it was either normal or only slightly elevated.

Renal Changes: Signs and symptoms of impaired renal function were present in all cases. Repeated urinalyses disclosed albumin and casts in the majority of the cases. In only one case were there signs of hematuria.

The blood urea nitrogen was in some cases moderately elevated. Only in three cases were there found levels above 100 mg. per 100 c.c.

At autopsy the kidneys disclosed changes described as arteriolar nephrosclerosis in various stages of development. In but three cases were there changes characteristic of accelerated nephrosclerosis. In one instance the diagnosis of chronic glomerulonephritis was made, and in another instance the diagnosis of chronic pyelonephritis was made.

Cardiac Changes: Clinical and pathologic studies of the heart showed, in all but one case, signs of hypertrophy and dilatation of the left ventricle.

Previous Attacks: A history of previous attacks was obtained in only four cases. Some of the attacks were transient "strokes"; others consisted of "dizziness" or transient loss of speech.

SUMMARY AND CONCLUSIONS

Attention is directed to an acute form of hypertensive brain disease with characteristic clinical and pathologic manifestations observed in a series of 12 cases.

The clinical picture is characterized by sudden onset and rapid progression of severe headache, drowsiness, confusion, restlessness and delirium, accompanied by signs of increased intracranial pressure, such as elevation of spinal fluid pressure and papilledema.

The gross and histologic examination disclosed in all cases findings characteristic of cerebral swelling.

The clinical picture presented is analyzed and discussed, and the rôle of cerebral swelling in the production of the acute clinical syndrome is emphasized.

It is proposed to designate the clinicopathologic syndrome as "hypertensive cerebral swelling," and to consider it as an acute form of hypertensive brain disease.

The view is expressed that cerebral swelling is caused by acute vasomotor disturbances, followed by vasoparalytic distention of the veins and capillaries and associated with increased permeability of the vessel walls for serous fluid.

Early recognition of the syndrome is of paramount importance because of the reversibility of the early stage of cerebral swelling.

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CASE REPORTS

TREATMENT OF PNEUMOCOCCAL MENINGITIS WITH SULFADIAZINE AND INTRATHECAL PENICIL- LIN G WITH RECOVERY *

By GARFIELD S. BARNET, M.D.† *Aspinwall, Pennsylvania*

PRIOR to the advent of chemotherapy, pneumococcal meningitis carried mortality of almost 100 per cent.^{1, 2} Sulfonamides lowered this depressing figure to some extent.³ Recent minimum mortality figures representing the results of combined sulfonamide and penicillin therapy approximate 40 per cent.⁴

The present case report was deemed worthwhile because of the following features:

(1) The progression of meningitis during the administration of intramuscular and intravenous penicillin.

(2) The exclusive use of crystalline penicillin G for intrathecal administration in concentrated solution without adverse reaction.

CASE REPORT

A 23 year old married colored laborer noted the onset of headache, fever, vomiting, and generalized aching pain, associated with a chilly feeling March 10, 1947. He later developed right pleuritic pain with increased fever and prostration. Symptomatic treatment provided no relief, he became progressively worse, and was referred to the Veterans Administration Hospital, Aspinwall, Pennsylvania on March 15, 1947. At the time of entry physical findings were as follows: Temperature 102.8° (R), respirations 40 per minute, pulse 140 per minute. Blood pressure 88 mm. Hg systolic and 58 mm. diastolic. The patient was acutely ill, well nourished, and showed grunting respiration with dilatation of the nostrils, slight drowsiness, and marked dehydration. Decreased expansion of the right chest was apparent; there were scattered inspiratory râles, bronchial breathing, and dullness over the entire right chest, most marked over the anterior lung field. There was no abdominal distention or nuchal rigidity. The abdominal and cremasteric reflexes were present, the Babinski was negative, but the ankle and knee jerks were absent.

Course. The blood pressure returned to normal limits within a few hours following intravenous infusions of glucose in saline. The patient was placed in an oxygen tent and given 100,000 units of penicillin intravenously. Blood culture showed 350 colonies of pneumococcus per c.c. Serologic tests for syphilis were negative. The initial white blood count was 8,300; differential—polymorphonuclears 97 per cent (metamyelocytes 6 per cent, juveniles 30 per cent, band forms 55 per cent, segmented 6 per cent), lymphocytes 3 per cent, moderate toxic granulation. The red blood count

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†Resident, Internal Medicine. The resident training program at the Veterans Administration Hospital, Aspinwall, Pa., is under the supervision of the Dean's Committee, School of Medicine, University of Pittsburgh.

was 4,750,000; hemoglobin 14.5 gm. Urinalysis was normal except for 1 + albumin and 8 to 10 red cells per h.p.f. General measures included fluid intake of at least 3,000 c.c. daily, oxygen, vitamin B parenterally, and vitamin C. Oral fluids were supplemented by frequent infusions. Specific therapy was as follows: Penicillin, 50,000 units every three hours intramuscularly from March 15 to April 1. Booster injections of 100,000 units of penicillin were given intravenously twice daily from March 15 to March 24 inclusive.

For three days signs of consolidation persisted over the entire right lung, and the rectal temperature varied from 101° to 103.4° F. Two days after admission the white blood count was 11,400; polymorphonuclears 73 per cent, lymphocytes 20 per cent, monocytes 2 per cent, eosinophiles 5 per cent. There was progressive drowsiness, and on the third day of hospitalization the lower abdominal reflexes and cremasteric reflexes were absent, and the knee jerks could not be elicited. There was marked nuchal rigidity, and the Brudzinski sign was positive. Lumbar puncture revealed cloudy fluid under increased pressure with 1,647 white blood cells per cu. mm. (100 per cent polymorphonuclears). The globulin test was markedly positive. Smear was negative for bacteria, and culture was sterile on a medium containing penicillinase. Oral sulfadiazine was initiated in a dose of 4 gm. March 18, and 1 gm. was given every three hours thereafter with equal parts of sodium bicarbonate until March 27 inclusive. Crystalline penicillin G was administered intrathecally twice daily March 18 and March 19 in doses of 20,000 units and once daily March 20, 21, 22, and 24. Twenty-four hours following the institution of the above therapy, the spinal fluid was under increased pressure and contained 1,117 white blood cells per cu. mm. (100 per cent polymorphonuclears). The spinal fluid sulfadiazine level was 5 mg. per cent. Rectal temperature was 101° F.; the pulse rate averaged about 100. On the following day the spinal fluid appeared grossly clear and contained 504 white blood cells per cu. mm. (100 per cent polymorphonuclears). The globulin test was moderately positive. Blood culture taken at this time was sterile (the medium contained both penicillinase and para-aminobenzoic acid). The patient appeared mentally alert for the first time, and his pulse was of good quality. On the next day the spinal fluid contained 99 white blood cells per cu. mm. (100 per cent polymorphonuclears), and the globulin test was still moderately positive. The rectal temperature averaged 101.2° F. There were now patchy areas of consolidation in the right lung with coarse râles of resolution. Slight neck stiffness was present, the abdominal reflexes were present, and the Brudzinski was negative. The patient appeared very alert and generally much improved. Urinalysis was now normal. One week after admission the lung revealed increasing evidences of slow resolution, the spinal fluid contained 49 white blood cells per cu. mm. (100 per cent polymorphonuclears), and the globulin test was only slightly positive. The patient was out of the oxygen tent for long intervals, was taking fluids well, and appeared quite comfortable. On the ninth hospital day the spinal fluid was clear, under normal pressure, and contained three white blood cells per cu. mm. The globulin test was negative. Thoracentesis in the eighth and ninth interspaces yielded only 3 c.c. of serous yellow fluid. Physical signs were consistent with patchy consolidation and areas of atelectasis in the right lung. Neurological examination was normal. The temperature continued to drop by lysis until March 30 from which point it remained normal. Serial chest roentgenograms revealed slow progressive resolution with marked pleural reaction. There was elevation of the right diaphragm but no mediastinal shift. Chest roentgenogram April 24 revealed complete clearing of the right lung field but persistent elevation of the right diaphragm. On this date the patient was asymptomatic and gaining weight. Repeated urinalyses were normal. The patient developed a hypochromic anemia with red blood counts varying between 3,430,000 and 3,840,000 cells per cu. mm. and hemoglobin varying between 11 and 13 gm. The

TABLE I

Date	Max. Temp.	Max. Pulse	Max. Resp.	WBC and Blood Culture	Spinal Fluid	Neurological	Treatment			
							I.M.	I.V.	I.T.*	Sulfadiazine
3/15	103.8° (R)	120	42	8,300 P—97 L—3 Toxic granulation 350 colonies pneumococcus per c.c.	—	Slight drowsiness, absent Achilles and knee jerks	50,000 U. every 3 hrs.	100,000 U. b.i.d.	—	—
3/16	101.4° (R)	120	48	—	—	—	50,000 U. every 3 hrs.	100,000 U. b.i.d.	—	—
3/17	102° (R)	90	40	11,400 P—73 L—20 M—2 E—5	—	Increasing drowsiness	50,000 U. every 3 hrs.	100,000 U. b.i.d.	—	—
3/18	103° (R)	98	35	—	1,647 cells/cu. mm. Globulin markedly positive. Pressure increased. Culture sterile	Stupor; positive Kernig and Brudzinski. Absent cremasteric and lower abdominal reflexes	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U. b.i.d.	4 gm. stat initially and 1 gm. every 3 hrs.
3/19	101.5° (R)	105	30	17,000	1,117 cells/cu. mm. 100% polys. Sulfadiazine level 5 gm. %	No change	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U. b.i.d.	1 gm. every 3 hrs.

TABLE I—Continued

Date	Max. Temp.	Max. Pulse	Max. Resp.	WBC and Blood Culture	Spinal Fluid	Neurological	Treatment			
							I.M.	I.V.	I.T.*	Sulfadiazine
3/20	101° (R)	105	28	Blood culture negative	504 cells/cu. mm. 100% polys. Globulin moderately positive. Grossly clear	Mentally clearer	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U.	1 gm. every 3 hrs.
3/21	101.6° (R)	105	24	12,900 P—81 L—18 E—1	99 cells/cu. mm. 100% polys. Globulin moderately positive	Slight nuchal rigidity. Abdominal reflexes present. Brudzinski negative. Patient alert	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U.	1 gm. every 3 hrs.
3/22	101.2° (R)	105	26	—	49 cells/cu. mm. 100% polys. Globulin slightly positive	No nuchal rigidity	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U.	1 gm. every 3 hrs.
3/23	100.6° (oral)	100	28	—	Not done	No change	50,000 U. every 3 hrs.	100,000 U. b.i.d.	None	1 gm. every 3 hrs.
3/24	100.4° (oral)	100	40	—	3 cells/cu. mm. Globulin negative. Pressure normal	Normal	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U.	1 gm. every 3 hrs.
	Temperature dropped by lysis and remained normal after 3/30				No further lumbar punctures performed	Remained normal thereafter	Continued until 4/1 incl.	100,000 U. 3/25 and 3/26	No further treatment	Continued to 3/27 incl.
						Totals:	6,800,000	2,100,000	160,000	80 gm.

* Intrathecal Penicillin G.

patient was discharged April 26, 1947 with instructions to take ferrous sulfate, 3 grains, three times daily.

The sequence of events and treatment are summarized in table 1.

DISCUSSION

Price and Hodges⁵ question the necessity for the intrathecal administration of penicillin and report two recoveries from pneumococcal meningitis using only the intramuscular and intravenous routes. However, the meninges are relatively impermeable to penicillin. After the parenteral administration of 100,000 units in normal individuals and in patients with meningitis, traces of penicillin are found in the spinal fluid for only brief periods.^{6, 8} In contrast, the spinal fluid titer remains high 24 hours after intrathecal injection.⁸ Consequently, many authors consider the intrathecal route essential.^{6, 2, 8, 9}

In retrospect, the areflexia of the lower extremities and the drowsiness noted at the time of hospital admission in this case probably indicated early meningeal involvement. Despite the administration of penicillin, 50,000 units intramuscularly every three hours, and 100,000 units intravenously twice daily in an infusion, clinically recognizable meningitis ensued. This occurrence is in harmony with the conclusions of those authors favoring the use of intrathecal penicillin.

Sulfadiazine has been advocated in pneumococcal meningitis^{6, 2, 4, 8} and was instituted as soon as the diagnosis was established. Booster doses of intravenous penicillin were employed because of the adverse prognostic significance of bacteremia,^{7, 3} and in an attempt to eliminate the focus of infection.^{7, 6} The administration of relatively large amounts of penicillin extrathecally will raise the spinal fluid concentration for periods up to one and one-half hours and thus might warrant less frequent intrathecal injections.⁸

Untoward reactions reported in cases receiving intrathecal penicillin by the lumbar route include neurogenic bladder and cauda equina disturbances,⁹ transverse myelopathy.¹ Intraventricular injections have produced convulsions^{6, 10} and vascular collapse.¹⁰

However in studies on normal human volunteers, spinal fluid pleocytosis, globulin rise, fever, and meningeal reaction were found to be minimized by careful technic.² The transverse myelopathy and neurogenic bladder could not be attributed unequivocally to penicillin, but occurred in patients treated for more than a week and/or receiving intrathecal doses of 40,000 units or more of penicillin daily. Intrathecal doses of 5,000 to 16,000 units every 24 hours will inhibit a standard strain of organism.^{2, 6} In Sweet's series there was no correlation between dosage and survival rate.⁹ Doses of 10,000 to 20,000 units intrathecally are well tolerated.^{8, 2, 3, 6, 7} Sweeney and Leslie¹¹ injected 30,000 to 50,000 units by the ventricular and lumbar routes without ill effect. Rotman-Kavka et al.¹² report no untoward reactions from lumbar intrathecal injections of commercial penicillin, crystalline penicillin G and penicillin X, provided the doses were less than 100,000 units and the periods of injection less than six weeks. However, Smith, Duthie, and Cairns⁶ believe that doses in excess of 20,000 units are not indicated.

Most investigators administer penicillin into the subarachnoid space in concentrations of 1,000 to 2,000 units per c.c.^{7, 3, 6} This involves the injection of relatively large volumes of fluid which seems undesirable in the presence of

infection and greatly increases the risk of contamination.⁹ Crystalline penicillin G is an effective agent against the pneumococcus.^{4, 12} It was felt that this highly purified fraction might be better tolerated than the amorphous penicillin. Intrathecal injections of crystalline penicillin G in concentrations of 10,000 units per c.c. of physiological saline caused no adverse effect in this instance. The volume of injected material was greatly diminished. The rise in spinal fluid white count and globulin reported by Smith et al.⁶ did not occur. The rapid therapeutic response recorded here is in accord with other reports which suggest that intrathecal penicillin is indicated in pneumococcal meningitis for periods of about five days in those cases demonstrating a good initial response.^{6, 8}

SUMMARY

1. A case of pneumococcal meningitis which developed during penicillin therapy of lobar pneumonia is presented, and the recent literature discussed.

2. Marked progression of the meningitis occurred until oral sulfadiazine and intrathecal penicillin G were administered, following which recovery ensued.

3. Crystalline penicillin G was injected intrathecally up to 20,000 units in relatively concentrated solution without adverse reaction, obviating large volumes of material and diminishing the risk of contamination.

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SYMPATHETIC PARALYSIS DUE TO METASTASIS AS INITIAL SIGN OF GASTRIC CARCINOMA*

By ABRAHAM WIKLER, M.D., Senior Surgeon, U. S. Public Health Service,
CARL WIESEL, M.D.,† and ELMER S. MAXWELL, M.D., Consultant in
Pathology, *Lexington, Kentucky.*

THE following case is of interest because the initial and, for almost two years, the only symptoms were those referable to a lesion involving the prevertebral thoracic sympathetic chain and adjacent intercostal nerves. Evidence of the metastatic nature of the lesion could not be found until a few months before death and autopsy alone showed that the stomach was the site of the primary tumor.

CASE REPORT

The patient, a 53 year old white male, was admitted to the U. S. Public Health Service Hospital, Lexington, Kentucky, on April 22, 1942, for treatment for drug addiction. The past medical history was essentially negative except for six attacks of "pneumonia" since 1928. The last episode occurred about March 25, 1942. Recovery was uneventful.

The present illness began about the time of his recovery from "pneumonia," in March 1942, when he began to have constant severe pain in the right breast. On June 12, 1942, he was admitted to the Neuropsychiatric Ward because of this complaint for which no local cause could be found. On questioning, the patient stated that the pain was "boring" or "stabbing," usually localized in the right nipple, although occasionally it seemed to originate in the right scapular region and radiate to the breast. Rarely it seemed to radiate to the right shoulder and down the inner aspect of the right arm to the elbow. It was aggravated by coughing, straining, sneezing and flexion of the neck.

Physical examination was negative except for persistent arterial hypertension (150 to 200 mm. Hg systolic, and 90 to 110 mm. diastolic) and early hypertensive changes in the retinal vessels. Repeated neurological examinations revealed only a mixture of hypalgesia and dysesthesia in the right D-4 to D-6 dermatomes. Urinalysis, blood counts, and repeated spinal fluid examinations with Queckenstedt tests gave results within normal limits. Blood and spinal fluid examinations were both negative for syphilis.

The Minor-Peet starch-iodine sweating test revealed anhidrosis of the right half of the face and neck, the right upper extremity and the right half of the chest down to about D-4. The presence of sympathetic paralysis was subsequently confirmed by a charcoal sweating test and plethysmographic studies. Because of the absence of miosis, ptosis and enophthalmos, it was evident that the lesions were localized between the first and fourth dorsal segments. Since there was no evidence of involvement of the spinal cord or of subarachnoid block, the lesion was considered to be extradural and probably extravertebral. Further evidence that peripheral nervous structures were involved was afforded by the histamine test described by Harris.¹ Approximately 0.1 c.c. of a 1:1000 aqueous solution of histamine phosphate was injected intracutaneously at intervals of about 2 cm. along the right axillary line in the vicinity of the fourth thoracic dermatome. Above the lower border of D-4 the local

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From the United States Public Health Service Hospital, Lexington, Kentucky.

† Formerly Passed Assistant Surgeon (R), U. S. Public Health Service.

wheal was present but the flare failed to appear. Below D-4, the usual wheal, flare and pseudopod formations appeared promptly.

Because of these findings, the bony structures and the posterior mediastinum of the upper thorax were investigated carefully. However, roentgenograms of the chest and thoracic spine were reported to be negative. Fluoroscopic examination of the chest after swallowing a barium meal revealed no evidences of a local tumor. Intravenous and retrograde pyelograms revealed no evidence of hypernephroma or other renal tumor.

The patient's symptoms continued unabated until posterior rhizotomy of the first to the seventh dorsal roots on the right side was performed by Dr. J. P. Evans, consulting neurosurgeon, for the relief of pain. Following the operation, the patient had no further pain, gained weight, and required no medication. The findings on physical and neurological examinations were the same as before with the addition of anesthesia from the first to the seventh dorsal dermatomes on the right side due to the operation. In December, 1943, while doing some light work, his right leg suddenly gave way and he fell. This caused an extracapsular fracture of the neck of the femur. He was placed in traction and the fracture healed with good position of the fragments.

In February, 1944, he complained of return of the right scapular pains, of "gas on the stomach" and pains over the kidney areas. On March 2, 1944, roentgenograms of the chest, taken routinely during a clinical tuberculosis survey in the hospital, revealed evidence of destruction and cyst formation in the right fourth rib, near the spine. In April, 1944, a small irregular nodular mass was palpated over the lower left rectus muscle. Biopsy was performed and the specimen was reported to be that of a metastatic adenocarcinoma, source unknown. A gastrointestinal series was then performed and on fluoroscopy there appeared to be a retroperitoneal mass which deformed the outline of the duodenum and pyloric end of the stomach. The patient's condition became progressively worse with weight loss, multiple complaints of pain, and edema of the legs and scrotum. He became stuporous and died on May 17, 1944, approximately 26 months after the onset of his illness.

The clinical impression was that the patient had a retroperitoneal tumor with metastases to the right fourth rib and adjacent sympathetic trunk, and to the abdominal wall.

PATHOLOGICAL FINDINGS

At autopsy a large irregular shaped tumor mass was found involving the posterior wall and lesser curvature of the stomach. The mass was fixed to the retroperitoneal tissues including the pancreas. The right paravertebral sympathetic chain was enmeshed in a dense fibrous tumor which occupied the right costovertebral angle and was adherent to the anthracotic right lung. This infiltrated the fourth rib and enmeshed the corresponding intercostal nerve (figure 1). Microscopic examination of the tumor in the wall of the stomach showed a carcinoma in which many of the cells were distended with mucus, forming typical signet ring cells. In other areas there was adenomatous arrangement of the cancer cells. The tumor tissue from the right costovertebral angle and from the decalcified rib showed an adenocarcinoma similar to that involving the stomach. Nerve trunks were found in the tumor involving the ribs and paravertebral spaces. There was extension of the cancer into the pancreas. The other pathological findings were not pertinent to this report.

The pathological diagnoses were: Massive adenocarcinoma of stomach (posterior wall and lesser curvature with extension to pancreas); metastatic carcinoma to right costovertebral area fourth rib and intercostal spaces (right), and subcutaneous tissue (lower right rectus muscle); hydronephrosis; lobular pneumonia; chronic passive congestion in liver, kidneys, and spleen; cardiac hypertrophy; atrophic changes in epithelium of thyroid; zones of liquefaction necrosis in left cerebral hemisphere (centrum ovale).

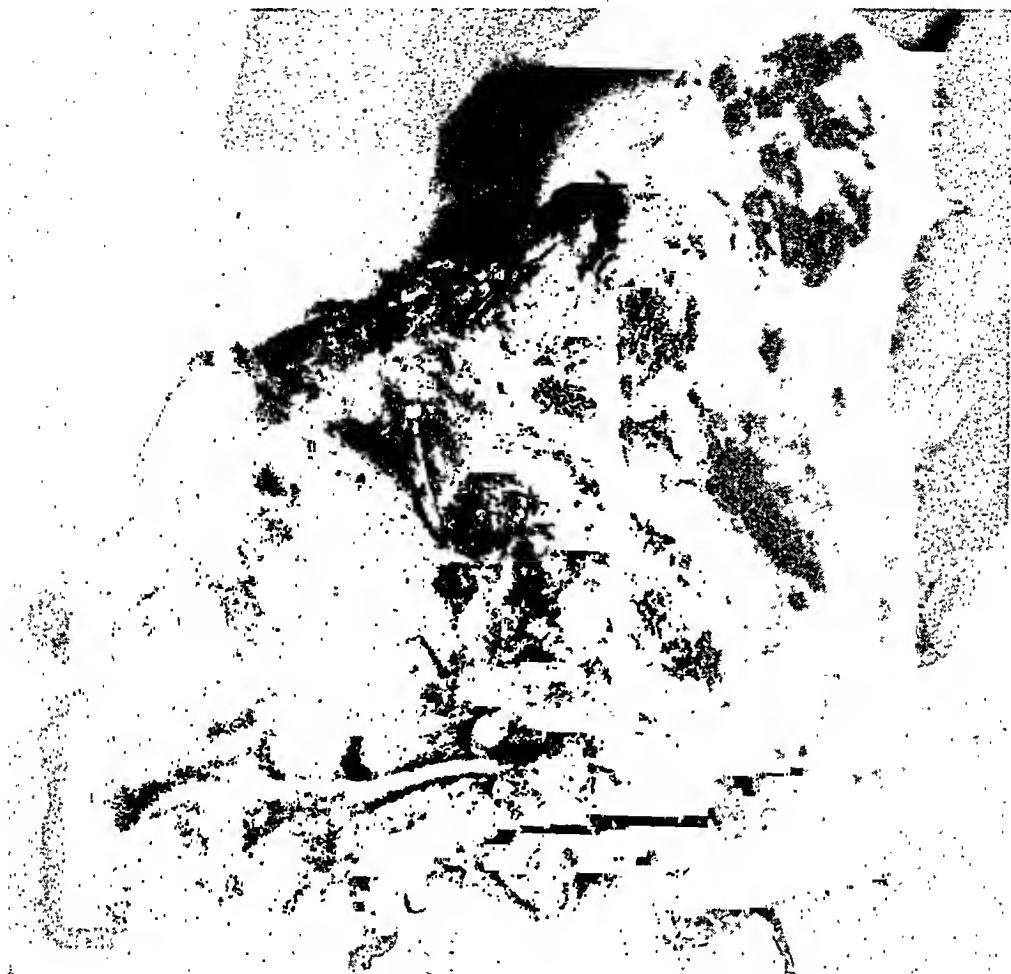


FIG. 1. Specimen showing metastatic tumor involving the right fourth costovertebral angle and corresponding intercostal nerves, with extension medially to involve the prevertebral sympathetic chain. The upper pin indicates the upper border of the tumor mass. The lower pin is placed in the sympathetic ganglionic chain.

COMMENT

The interesting feature of this case is the long interval (about two years) between the onset of symptoms due to metastasis and evidence of disease of the stomach, which was the site of the primary lesion. In this connection it may be emphasized that, where metastatic tumor is suspected, the gastrointestinal tract should be investigated even though there are no gastrointestinal symptoms. Whether or not the metastases involved the bony structures first and the nervous structures secondarily could not be determined with certainty. Bone metastasis as the initial sign of carcinoma of the stomach is rare but does occur occasionally.² However, the bulk of the metastatic tumor mass was found in the soft tissues about the prevertebral sympathetic chain and the adjacent intercostal spaces. Also, spot films of the bony structures which were subsequently involved were negative for at least one year after the onset of sympathetic paralysis. Therefore, it appears more probable that the prevertebral soft tissues with their nervous structures were invaded first by this metastatic tumor.

SUMMARY

1. A case is reported in which symptoms due to metastasis from carcinoma of the stomach to the prevertebral soft tissues, involving the sympathetic chain and adjacent intercostal nerves, antedated by about two years any symptoms or signs referable to the gastrointestinal tract.

2. It is emphasized that the possibility of carcinoma of the stomach should be investigated where the clinical evidence indicates a localized neoplastic lesion, even though there are no gastrointestinal complaints.

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PROGRESSIVE COCCIDIOIDOMYCOSIS: REPORT OF A CASE *

By NORMAN A. HARVEY, 1st Lt., Medical Corps, A.U.S., *Brooklyn, New York*

THE purpose of this report is to present another case of progressive or disseminated coccidioidomycosis with clinical data and autopsy findings, together with a brief discussion of some aspects of the disease.

CASE REPORT

On January 4, 1946, a 24 year old white male was admitted to the Pasadena Regional Hospital, complaining of pain in his left chest, shortness of breath, marked fatigue, and bouts of chills and fever.

His illness dated back to August 1945 when he made two trips to the San Joaquin Valley driving a truck. He stayed there about one day each time. Approximately two weeks after the last trip, he developed constant frontal headaches, marked lassitude, and fever, and by September 10, 1945 had a fever as high as 104° F. with chills. He was hospitalized on September 11, 1945. Roentgenograms of the chest and malaria smears taken at this time were negative. Symptoms continued, and on or about October 10, 1945 he developed constant aching pains in the left chest and roentgenographic evidence of fluid in the left pleural space. An intradermal skin test with coccidioidin (1:100 dil.) was strongly positive. Blood specimens were sent to the laboratory of the coccidioidomycosis study of the Commission on Epidemiological Survey, Board for the Investigation of Epidemic Diseases, Preventive Medicine Service, Office of the Surgeon General at Stanford Medical School. The first sample, dated November 26, 1945, showed a positive complement fixation test up to a 1:8 dilution. A second sample, dated December 19, 1945, also was positive for complement fixation in a dilution of 1:8, but the precipitin test was now negative. The conclusions of this laboratory were that there had been no significant change in the titer of the antibodies and that stabilization of antibody production at this moderate level indicated that the infection was being well handled.

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Clinical records from this hospital were not available, but the patient stated that he received sulfadiazine, followed by penicillin, without improvement.

On January 4, 1946, the patient was transferred to the Pasadena Regional Hospital. Physical examination on admission revealed a well developed, poorly nourished, young, adult white male, who appeared chronically ill. Temperature on admission was 101° F., pulse 84 per minute, and respirations 24 per minute. There was diminished resonance over the entire left chest, with only faintly audible breath sounds over the same area. No râles were heard. There was moderate pallor of the mucous membranes. A complete hematologic examination showed a red cell count of 3.5 million, hemoglobin of 11 gm., and a white cell count of 4,750 with a differential of 62 per cent neutrophils, 35 per cent lymphocytes and 3 per cent monocytes. The sedimentation rate was 11 mm. in 45 minutes (Osgood and Haskins modification of Westergren's method). The urine was normal. Roentgenogram of the chest showed an area of increased density obliterating the lower third of the left hemithorax and was believed to represent pleural thickening and effusion (figure 1a). There were very small areas of decreased density scattered through this area which resembled cavity formation. Skin tests with intradermal coccidioidin were repeatedly negative, using a 1:100 dilution. Tuberculin tests were positive with a 1:1000 and 1:100 dilution (one plus and two plus respectively). A blood sample sent to the laboratory of the coccidioidomycosis study of the Commission on Epidemiological Survey, Board for the Investigation of Epidemic Diseases, Preventive Medicine Service, Office of the Surgeon General at Stanford Medical School, revealed a positive complement fixation test in a 1:8 dilution. (The precipitin test could not be run because of contamination.) The conclusions of that laboratory were as follows: There has been no significant change in serology which is reassuring in view of clinical severity and apparent anergy. The latter is rather alarming (he previously had good reactivity).

Repeated gastric lavage specimens were negative for acid-fast bacilli, both by smear and culture. Blood culture planted on blood agar, brain heart infusion broth, and Sabouraud's glucose agar were repeatedly negative for bacteria and fungi. Aspirated pleural fluid failed to grow out any organisms on two occasions. No sputum was obtainable at any time.

Serial roentgenograms of the chest showed a slight clearing of the pleural effusion in the left lower chest (figures 1b and 1c), but otherwise no essential change. The right lung remained roentgenographically negative. Survey films of the long bones showed no abnormalities, and a flat plate of the abdomen was negative.

Hematologic studies revealed a persistent, mild hypochromic anemia, mild acceleration of the sedimentation rate, and mild leukopenia. The blood non-protein nitrogen, urea nitrogen and chlorides were within normal limits. The serum protein was 5.2 gm. per 100 c.c. of blood, with an albumin of 2.8 gm. and a globulin of 2.4 gm.

Clinical Course: The patient's course was progressively downward. There was a constant temperature elevation which initially ranged from 99° F. to 102° F. to 104° F., and during the last two weeks of life, from 103° F. to 105° F. There was progressive weight loss, fatigue, and cachexia. The patient was given a course of penicillin therapy, and received a total of 6,260,000 units in doses of 40,000 units, then 60,000 units intramuscularly every three hours, with no clinical improvement nor effect on temperature. He was treated with repeated blood transfusions, intravenous glucose, plasma and physiological saline, and a high caloric, high vitamin diet. One hundred c.c. of amino acids were given intravenously three times daily, plus 12 mg. of vitamin K by mouth. On January 24, 1946, the patient first gave evidence of apparent involvement of the central nervous system, manifested by emotional disturbances, suicidal intent and generalized tremors. About one week later, he became delirious and incontinent of urine and feces. Respirations became shallower and more rapid, and the patient appeared to have respiratory distress, but was not cyanotic. On February 10,

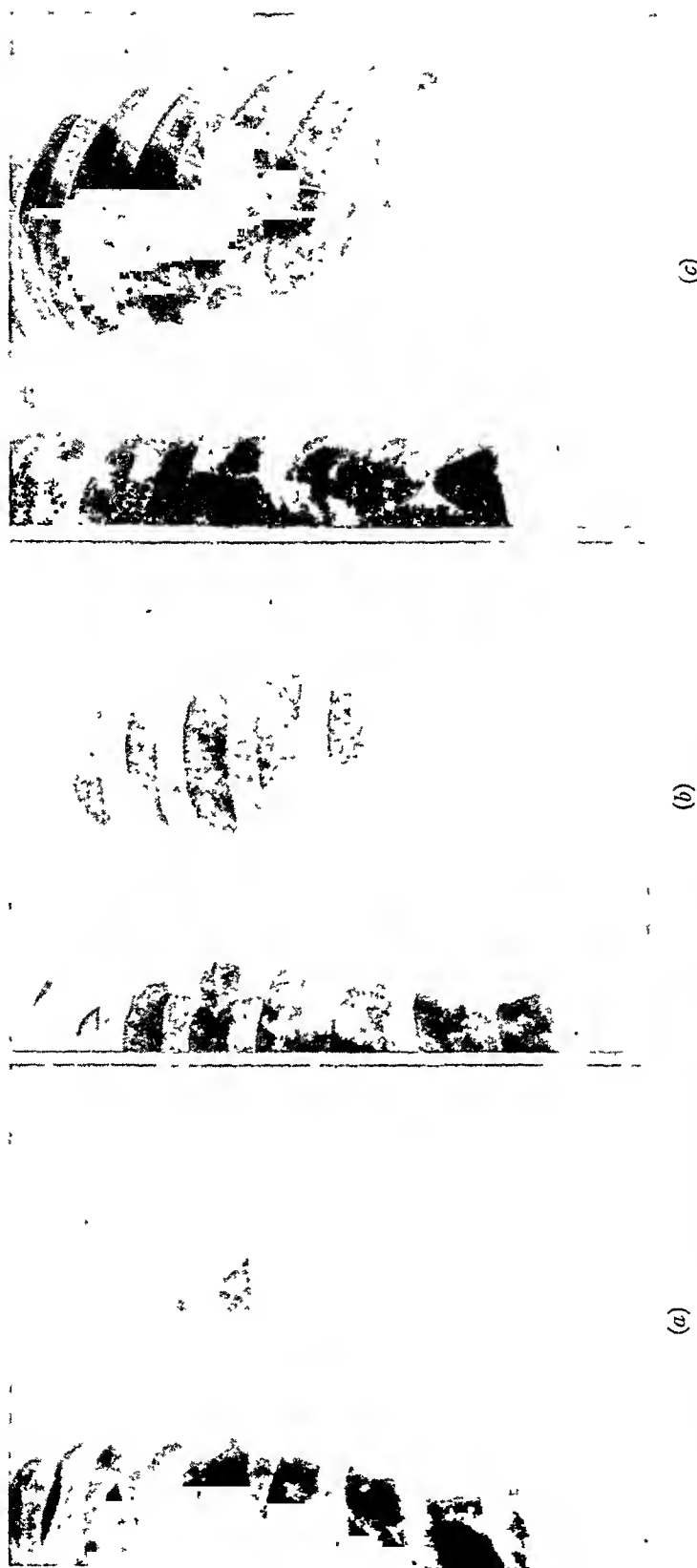


FIG. 1. (a) Roentgen-ray film of chest dated January 4, 1946. Interpreted as pleural effusion and thickening. (b) January 26, 1946. Effusion clearing. (c) February 4, 1946. Some fluid remains in left costophrenic angle. Pulmonary lesion now shows up well.

the patient became stuporous and finally lapsed into coma. There were generalized body tremors, hyperactive deep reflexes with bilateral patellar and ankle clonus, and there was marked rigidity of the neck. A spinal puncture showed a clear fluid under no increased pressure. Smear and culture revealed no organisms. There were six leukocytes per cu. mm.; the glucose and protein values of the spinal fluid were normal. Two days before death the abdomen became distended, and the patient became jaundiced. The patient died on February 13, 1946 at 0245, following a spell of vomiting.

Necropsy Report (Condensed)

A. Gross: Lungs. The right pleural cavity contained about 50 c.c. of blood-tinted fluid; the left was completely obliterated by dense fibrous adhesions. In the upper medial aspect of the left lower lobe there was a rounded firm node measuring 1.8 by 1.6 by 1.2 cm., composed of semicaseous, greenish-gray material and delimited by a dense dark red-gray layer up to 3 mm. thick. A smaller node, 7 mm. in diameter, was located below the first, which it resembled except that it was not well delimited and was surrounded by a few scattered pinhead size nodules. The cut surfaces of the lung in general were mottled uniformly by many tiny pinpoint size translucent gray nodules, and were dark red and moist with frothy fluid. The right lung answered to a similar description except that no larger nodes were found. The mucosa of the bronchi was moderately injected. A few tracheobronchial lymph nodes were enlarged to a lima bean size and were semicaseous.

Peritoneal Cavity. This contained about 500 c.c. of cloudy yellow fluid mixed with flakes of fibrin. The peritoneal surfaces were covered with patchy membranes of fibrin, especially the serosa of the small intestine. The greater omentum was thickened and indurated, and its cut surface was mottled by irregular grayish patches. The surface of the liver was covered by a thick layer of gray-yellow exudate.

Spleen. The spleen weighed 400 grams. It was surrounded by fibrinous exudate and was partly adherent to the diaphragm. The capsule was dark purple-red and studded by irregular grayish yellow nodes varying from a few mm. to 2 cm. in diameter. The cut surfaces presented a similar picture and were mottled by numerous large and small nodes up to 2.5 cm. in diameter. Some of the nodes on the capsule were semiliquid and partially disintegrated, and the necrotic material had spread into the peritoneal cavity.

Liver. The liver weighed 1600 grams. The capsule was covered with a thick layer of grayish-yellow caseous and fibrinous exudate, and was studded by scattered nodes which resembled those described in the spleen. Some of the nodes had broken down and the necrotic material was continuous with the exudate on the surface. The cut surfaces of the liver were studded by occasional nodes similar to those in the spleen.

Pancreas. The pancreas weighed 120 grams, and was normally firm and lobular. A few peripancreatic lymph nodes were enlarged to navy bean size and were composed of pale gray-yellow semicaseous tissue.

Kidneys. The right kidney weighed 200 grams, and the left kidney 180 grams. The cortex was grayish red and hyperemic, and the differentiation was only fair. Otherwise the kidneys were grossly normal.

Brain. The brain weighed 1600 grams. There was an increased amount of clear intermeningeal fluid. The leptomeninges were thin and transparent. The cortex and basal ganglia were pale and gray. The white matter was edematous and injected. The lateral ventricles were slightly dilated with clear fluid and the ependyma was smooth.

B. Microscopic: Lungs. The large node described above in the lower lobe of the left lung consisted of finely granular, eosinophilic, caseous, necrotic material sur-

rounded by a thin, partly hyalinized fibrous capsule. It lay near the pleural surface from which it was separated by a thin rim of compressed atelectatic lung. Adjacent to the large nodule and scattered through the lung were many smaller, similar areas of necrosis. There were occasional Langhans' giant cells and doubly-contoured coccidioidal spherules in the granulomatous tissue surrounding these caseous areas. Some of the smaller foci were in an early stage of development and showed a small central area of suppuration containing polymorphonuclear leukocytes and granular, necrotic tissue debris surrounded by a hyaline change in the fibrous stroma. The older lesions were larger, showed a granulomatous reaction, and the cellular infiltrate consisted mainly of lymphocytes and plasma cells, with a few epithelioid cells and giant cells toward the middle. The largest lesions had a caseous center. Many *Coccidioides immitis* organisms were seen in and around the various lesions, most of which were in the spherule stage, but a few were enlarged and showed endospore formation. Between these foci of infection, the lung parenchyma showed edema, atelectasis, blood in the alveoli, hemosiderin ingestion by macrophages and patchy areas of fibrosis and lymphocytic infiltration. The pleura contained small nodules of granuloma and also was diffusely thickened with granulation tissue.

Tracheobronchial nodes. These were filled with large areas of caseous necrosis surrounded by fibroblastic proliferation containing giant cells, plasma cells and lymphocytes, though occasionally polymorphonuclear leukocytes predominated. Numerous organisms were seen in the latter areas.

Liver. There were numerous foci of caseous necrosis surrounded by granulomatous tissue. Many *Coccidioides immitis* spherules and large endosporulating forms were seen along with numerous giant cells. In addition, there were large confluent areas of suppuration and tissue necrosis in which the polymorphonuclear leukocytes predominated, and numerous organisms were seen. Around these foci there was as yet little fibrous proliferation.

Spleen. This presented a picture similar to that of the liver but with a relatively greater amount of acute necrotic suppurative reaction than of granuloma production.

Kidneys. One small area of necrosis and suppuration was seen, with both sporulating and non-sporulating types of organisms. Elsewhere there were small foci of fibroblastic proliferation infiltrated with plasma cells and a few polymorphonuclear leukocytes. Interstitial hyperemia was present.

Brain. This showed edema, hyperemia and focal areas of pyramidal cell degeneration. The white matter was edematous and hyperemic. The meninges were normal in appearance.

CASE COMMENT

This case of progressive coccidioidomycosis had several instructive features. The history indicates how a short contact with the infected dust can give rise to the severe disseminated infection. The patient was a white person, in whom the progressive form of the disease appears to be much less common than in colored races.^{16, 20} Stabilization of antibody production at a moderate level was misleading in that such a finding often indicates that the infection is being adequately localized by the immune forces of the body (see laboratory report above). The development of skin energy to coccidioidin in the disseminated stage of coccidioidomycosis, together with the positive tuberculin test, as seen in this case, is a combination for clinicians to guard against, lest they interpret this as indicating the presence of active tuberculosis and the absence of coccidioidal infection. The converse of this picture might also occur in endemic coccidioidal areas in a patient with miliary tuberculosis. In both diseases, so similar clinically and

roentgenographically, the disseminated form frequently is associated with skin anergy.^{5, 6, 16, 20}

The presence of a large, subpleural caseous nodule in the left lung with caseation of the tracheobronchial lymph nodes suggests a primary infection closely analogous to the primary tuberculous complex of Ranke with the Ghon tubercle.* The subsequent lymphatic and hematogenous spread to the abdominal organs and remaining lung tissue presumably took place in a manner analogous to that of miliary or disseminated tuberculosis.

Coccidioidomycosis of the peritoneum occurs in the disseminated disease by hematogenous spread as does tuberculosis of the peritoneum in miliary tuberculosis.²⁰ In this case there was an acute, generalized, exudative peritonitis due to intraperitoneal rupture of caseous liquefying nodules on the surface of the spleen and liver, analogous to a generalized tuberculous peritonitis.¹⁷

Coccidioidal meningitis is a common terminal feature of the disseminated form of the disease, especially in the white race.^{1, 2, 6, 16, 20} Abbott and Cutler¹ believe that it occurs in about 25 per cent of fatal cases, while Ash and Spitz² feel that it is even more common. The symptoms in this case were due to diffuse parenchymal damage to the central nervous system rather than meningitis, although the signs were suggestive of the latter condition. Failure to isolate the organisms from the spinal fluid is frequent even in frank cases of meningitis. The colloidal gold curve is often of the paretic or first zone type and the cell count varies from 50 to 200 cells per cu. mm. with about 75 per cent lymphocytes.^{1, 18}

Penicillin was used in doses of from 40,000 to 60,000 units intramuscularly every three hours up to a total of 6,260,000 units, with no demonstrable effect on the clinical course. Michael et al.¹⁸ have previously reported a penicillin failure using a total of 3,081,000 units.

DISCUSSION

The concept of coccidioidomycosis has undergone considerable change since the first case reports. These early workers believed it to be a rare protozoan infestation.^{19, 25} When the etiologic agent became known the disease was thought to be an uncommon, highly fatal fungus infection.^{4, 7} It is now recognized as a common (in endemic areas), usually benign, pulmonary reaction to the inhalation of infective dust, self-limited and often subclinical, but which may resemble a common "cold" or the "flu" for which it is frequently mistaken.^{4, 5, 6, 8, 9, 16, 20}

Etiology. The etiological agent, *Coccidioides immitis*, appears in two forms. one on culture media and one in the tissues of the animal host. The tissue or parasitic phase is a protoplasmic spherule with a thick, doubly contoured wall, and measures 10 to 60 μ . in diameter. As this spherule becomes larger, it develops 50 to 100 endospores which break out of the capsule and repeat the process. In the saprophytic phase, the organism develops on a variety of media as a mould-like growth with the production of a white, cottony, aerial mycelium, which turns tan with age. Microscopically the mycelium consists of branching septate hyphae, which later become segmented into oblong or rounded spores

* Butt and Hoffman⁴ observed healed calcified primary pulmonary lesions of coccidioidomycosis at autopsy and reported that they were indistinguishable from those of calcified primary tuberculosis.

(arthrospores). These spores are the highly infective form of the organism and are found in the dusts of endemic areas.^{5, 6, 8, 9, 16, 20}

Geographic Distribution. By means of the skin test, Army medical personnel have outlined endemic areas in the southwestern United States, including the great central valley of California north to Madera, the western slope of the Coastal Range, all of Arizona and New Mexico, southern Utah, southern Nevada, west Texas, and northern Mexico. Isolated cases have been reported in northern, central and eastern United States. Hawaii has been implicated as well as the Chaco region of Argentina and Uruguay.^{20, 25} Smith feels that the arid regions of the Near East, Mongolia and Australia also deserve further investigation.²⁰

Epidemiology. The cause of the endemicity has been in doubt. There is no evidence of direct patient to patient infection. The organism has been isolated from the soil in endemic areas, but with difficulty owing to a sparse, highly spotty distribution.¹⁰ Because of these facts, Emmons was led to look for an animal reservoir which he believes he has found in the wild rodent population of endemic areas.^{10, 11, 12} He suggests examination and culture of lungs from samples of the rodent population as a quick, dependable method for determining the presence or absence of *Coccidioides immitis* in a specific locality. If valid, this method has a theoretical advantage over the skin test in that it is a more direct measure of an infective area, and therefore will be more sharply delineative, whereas the skin test, which is indirect, will be influenced by migration of the inhabitants of the region. Dickson,⁸ Dickson and Clifford⁹ were among the first to recognize the fact that there was a common, benign form of coccidioidomycosis, and that the disease known as "San Joaquin," "Desert," or "Valley" fever was the primary coccidioidal infection accompanied by erythema nodosum. This skin phenomenon is seen in 3 to 5 per cent of the cases and is believed to be a hypersensitive manifestation of a freshly acquired allergy.^{20, 21} The allergy is of long duration and appears to confer lasting immunity to a second similar infection and to the progressive form of the disease as well.^{16, 20, 21} In the San Joaquin Valley, Smith²¹ found a seasonal variation in "Valley" fever with a peak in the dusty fall and a low incidence in the wet winter. He also observed that this manifestation is most common in white females and in newcomers to the region. Four-fifths of the long time residents in the Southern San Joaquin Valley give a positive coccidioidin skin test.^{20, 21} There is a higher incidence (four to seven times) of progressive coccidioidomycosis in males and there is marked predilection of the disseminated form for the dark-skinned races, e.g., Filipinos, Negroes and Mexicans.^{2, 6, 20, 21}

Pathogenesis. In most cases, infection is caused by inhalation of dust containing infective arthrospores. Dusty objects such as hay, clothes, camping equipment, etc., when carried from an endemic area, can infect persons in remote noninfected areas. Rarely the skin is the portal of entry.

Pathology and Roentgenographic Findings. The majority of infections are benign and self-limited; therefore, early human pathological material is lacking. Dickson and Clifford⁹ report that guinea pigs and rabbits forced to inhale the spores, develop a transient interstitial pneumonitis, which shows the same hilar and parenchymal shadows on the roentgenogram as does the primary infection in humans. According to these workers, the initial reaction is an irritation of the lymphatics which does not cause necrosis or granuloma production. Clark and Gilmore⁵ feel that the initial pulmonary infiltration associated with the pri-

mary infection has a distinctive roentgenographic pattern by which it may be differentiated from early adult tuberculosis. They stress the relatively marked hilar or mediastinal adenopathy in primary coccidioidomycosis which is lacking in adult (superinfection type) tuberculosis. The roentgenographic picture, however, is frequently indistinguishable from bronchopneumonia or primary tuberculosis, and at times the sharp outline of the shadow suggests metastatic malignancy.^{16, 20} The lung infiltrations often disappear entirely but may occasionally leave fibrosis as a round or linear scar.⁵ Reinfection apparently seldom occurs. In more severe pulmonary involvement, there may be an extensive caseous pneumonia, perhaps with cavity formation. However, even these extensive pathological changes, which would give a grave prognosis in tuberculosis, tend to resolve completely on bed rest and other supportive measures.^{5, 6, 16, 20} The progressive form of the disease may come after widespread lung involvement, or may originate from a relatively small focus. The symptoms are referable to organs showing massive lesions, especially lungs, bones, lymph nodes, meninges and occasionally skin. Clinically, by roentgen-ray, and in anatomic distribution, the visceral lesions may closely resemble tuberculosis, blastomycosis, or one of the lymphomas.² Subcutaneous and multiple "cold" abscesses seem to be more frequent in coccidioidomycosis than tuberculosis.²⁰

Histologically the early lesions are mostly purulent with some necrosis, surrounded by plasma cells, lymphocytes, a few monocytes and connective tissue showing hyaline change. The older lesions are granulomatous, containing epithelioid and giant cells and frequent caseation. The healing or healed stage consists of replacement by a fibrous scar and sometimes eventual calcification.² Areas containing many organisms, both sporulating and non-sporulating, may present a more acute suppurative and necrotic picture, whereas areas with only a few organisms show chronic granuloma production (figure 2). The non-sporulating spherule of *Coccidioides immitis* is practically indistinguishable from the non-budding form of *Blastomyces dermatitidis*, and animal inoculation may be necessary in cases of doubt.^{2, 6, 20}

Immunology. A specific soluble substance was found in liquid cultures of *Coccidioides immitis* by Hirsch and Benson¹⁴ which gave reliable positive skin tests in infected animals and humans. This substance is dialyzable, relatively heat stable, and is probably a polysaccharide.²³ It has been standardized in skin test units²³ and has been shown to give no cross reactions in cases of tuberculosis¹⁵ or blastomycosis.⁴ Sensitivity to coccidioidin usually develops 10 days to one and one-half months after acquiring infection.²⁰ Butt and Hoffman⁴ feel that the intradermal coccidioidin skin test has the same clinical significance as the intradermal tuberculin test, but Stewart and Kimura²³ warn that the skin test should not be regarded as absolutely specific until the antigenic cross relations and the generic position of the organism are established. Skin test with coccidioidin in the Middle West and a few Eastern states have shown some doubtful and some definite positives which may be due to cross reactions with other fungus disease.²⁰ Histoplasmosis is endemic in the Middle West. Emmons and Ashburn¹² believe that *Coccidioides immitis* and *Haplosporangium parvum* are antigenically related, although they found that experimental *Haplosporangium* infection in mice did not protect against subsequent infection with *Coccidioides immitis*.³ Regardless of theoretical objections, the skin test is widely used as a practical, clinical and epidemiological procedure.

Serological studies have also proved valuable. The complement fixation and precipitin reactions have been employed and appear to correspond, in a general way, to the extent of the disease process. Thus, the mildest cases usually show no demonstrable antibody production.^{6, 20} The more severe, but still localized cases, often show a rise in precipitins which may fall as the complement fixation titer rises. Precipitins are poorly demonstrated in most disseminated infections,

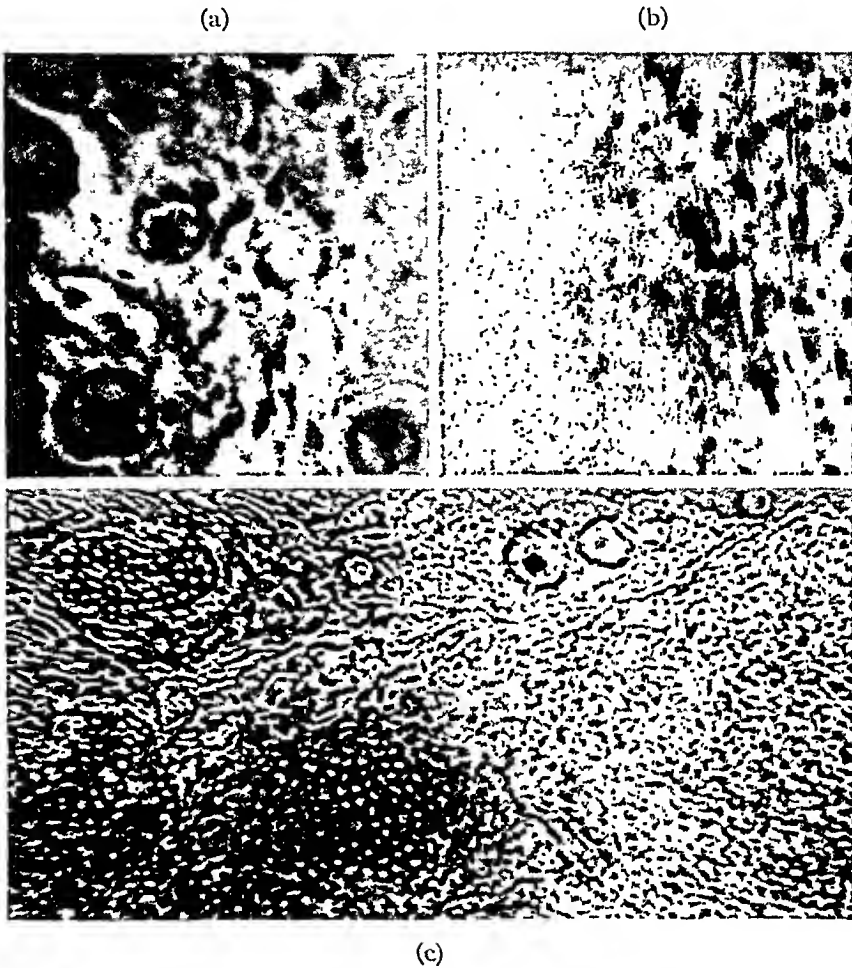


FIG. 2. (a) Spherule stage of *Coccidioides immitis*, tracheobronchial lymph node. $\times 450$. (b) Edge of caseated area, tracheobronchial lymph node. $\times 400$. (c) Spleen, numerous endosporulating organisms, with acute necrotic reaction. $\times 350$

probably because precipitins are generally transient and dissemination usually occurs later in the course of the disease, at which time the precipitins may have already disappeared. When healing occurs (as in the vast majority of instances), the complement fixation falls. The precipitins may remain high for a time but usually disappear before the complement fixing antibodies. A rising, or persistently high complement fixation test, is usually interpreted as indicative of dissemination.^{20, 22} In some disseminated cases, fixation of complement may occur completely even in dilutions up to 1:256 or higher.²⁰ Dr. C. E. Smith of Stanford University feels that no hard and fast rules for the interpretation of serological tests can be set because there is such an individual variation in anti-

body response, and urges that serologic data be closely correlated with clinical findings.²²

Therapy. There appears to be no specific therapy as yet. Penicillin was given in this case with no demonstrable effect, and Michael et al.¹⁸ reported a failure with 3,081,000 units.* Sulfonamides have been found useless. Arsphenamine, iodides, gentian violet, etc., have all been tried without beneficial effect.^{16, 20} Desensitization to coccidioidin along with injections of colloidal copper were tried by one worker with promising results.⁶ Goldstein and McDonald¹³ report a possible therapeutic success in one case using transfusions of convalescent blood but admit that no conclusions could be drawn from one case. Smith²² has tried similar "immunotransfusions" with no favorable results and feels that ordinary transfusions may be just as beneficial. Salicylates are useful in the hyperergic type of primary infection with erythema nodosum and painful joints.²⁰ Bed rest and conservative supportive therapy will cure most cases of primary pulmonary infection, even with large cavity formation.^{6, 16, 20} Collapse therapy is occasionally necessary, and artificial pneumothorax is preferable to the major procedures. Once dissemination has occurred the prognosis is rather poor, depending of course upon the sites of dissemination, with about a 50 per cent fatality rate. Smith²⁰ believes that strain difference in the organism is not responsible for the variation in severity of infection, but that such variation is apparently dependent upon racial, sexual, familial and individual factors, as well as the inoculating dose of the organism. Efforts should be made as early as possible to give rest and general supportive treatment to assist the patient in focalizing the infection.

SUMMARY

A case of progressive coccidioidomycosis is presented with clinical data and necropsy findings. A generalized coccidioidal peritonitis found at autopsy was apparently caused by the intraperitoneal release of infective material from necrotic liquefying nodules on the surface of the spleen and liver. The complement fixing antibodies never gave a positive test in dilutions greater than 1:8, and the patient became anergic to intradermal injections of coccidioidin (1:100 dil.) in the terminal stages of the disease. A total of 6,260,000 units of penicillin was given with no demonstrably beneficial clinical effect. Many analogies can be drawn between coccidioidomycosis and tuberculosis. A brief discussion of some aspects of the disease is presented.

ACKNOWLEDGMENT

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PULMONARY ASPERGILLOSIS: REPORT OF TWO CASES *

By B. GERSTL,† *Hartford, Connecticut*, WILLIAM H. WEIDMAN,‡ *F.A.C.P.,
Norwich, Connecticut* and ABBOTT V. NEWMANN †

A VARIETY of symptoms and roentgenographic changes have been reported as indicative of pulmonary aspergillosis. This suggests that there may be considerable variation in the individual response of the host to the invading microorganism. Cases of primary and uncomplicated pulmonary aspergillosis have been described which by their course and roentgen-ray appearance simulated tuberculosis^{1,2} whereas others behaved like an acute lobar pneumonia.³

In the two cases to be reported an aspergillus was the sole or predominant infective agent. Symptomatically and in roentgen-ray appearance, however, these cases differ markedly. This emphasizes the dissimilarity of signs one may encounter in this disease.

Case 1. The first patient was a 33-year-old housewife. She had had left sided pneumonia, with pleurisy, in 1927. In 1932 there was an episode of hemoptysis. No evidence of tuberculosis was found on clinical and roentgenographic examination. The patient remained in apparent good health until 1936 when she developed symptoms of a "chest cold." A chest film at this time revealed the presence of a 1 cm. density, productive in character, at the level of the second anterior rib on the left side. Just below this was a smaller productive nodule. She entered a sanatorium for three months.

Following her discharge another hemoptysis occurred and she came to the Cedarcrest Sanatorium, Hartford, Connecticut in August 1937. She was discharged two months later as non-tuberculous. She then remained asymptomatic except for intermittent small hemoptyses. When roentgen-rayed on March 29, 1940 at the Undercliff Sanatorium, Meriden, Connecticut, a uniform area of faint radiopacity was noted below the left clavicle, between the fifth and seventh ribs posteriorly, measuring about 3 cm. (figure 1). Infrequent small hemoptyses continued until May 1943, when the bleeding became profuse. After two days in a local hospital she transferred to the Undercliff Sanatorium on May 19, 1943.

Course in the sanatorium: With laminographic studies no definite cavity could be discovered within the infiltrative process involving the left upper lobe, although small areas of lesser density were seen in the 8 and 10 cm. planes. The left upper lobe bronchus was clearly visualized as running along the inferior border of the area of infiltration.

Laboratory findings: Red blood cells were 3,190,000, hemoglobin was 64 per cent, white blood cells numbered 9,900 with polymorphonuclears 76 per cent, eosinophiles 1 per cent, lymphocytes 13 per cent and monocytes 10 per cent. Urine specimens were negative. The patient expectorated little and the sputum was negative for tubercle bacilli both by culture and guinea pig inoculation.

A left pneumothorax was induced one month after admission to control hemoptyses. Following this, the patient had slightly blood streaked sputum without frank hemoptysis. The pneumothorax was not maintained and the left lung had fully re-expanded by roentgen-rays of October 12, 1943. The following day she began another series of hemoptyses. On October 19, a left phrenic crush was performed with the

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† Central Laboratory of Pathology and Research, State Tuberculosis Commission, Hartford, Conn.

‡ Uncas-on-Thames Sanatorium, Norwich, Conn.

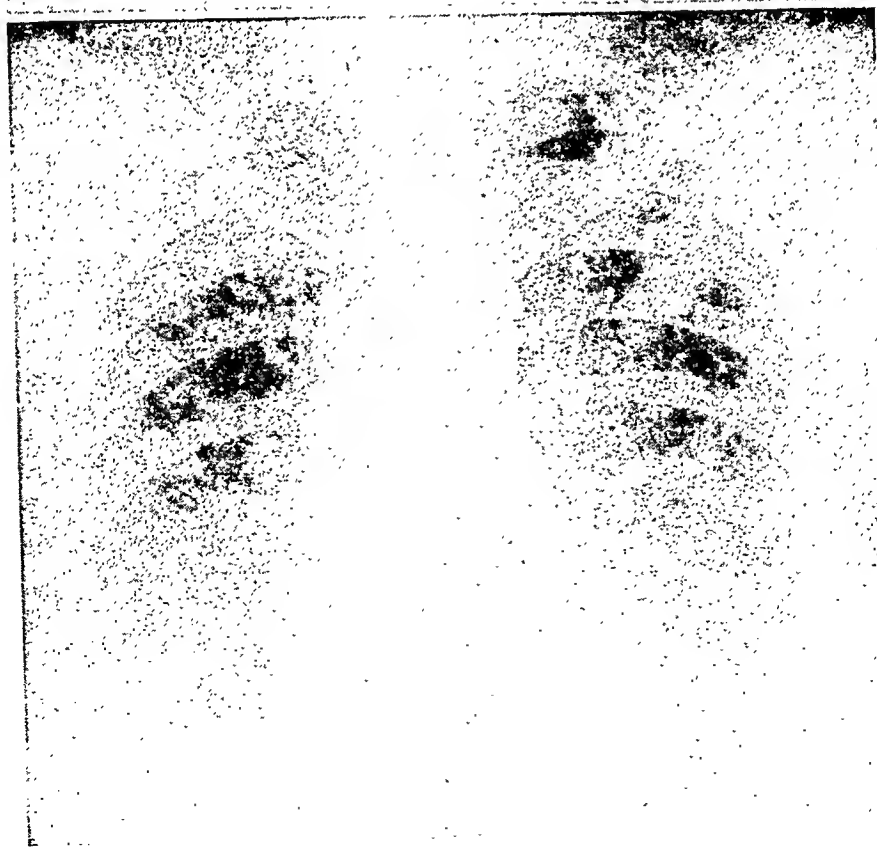
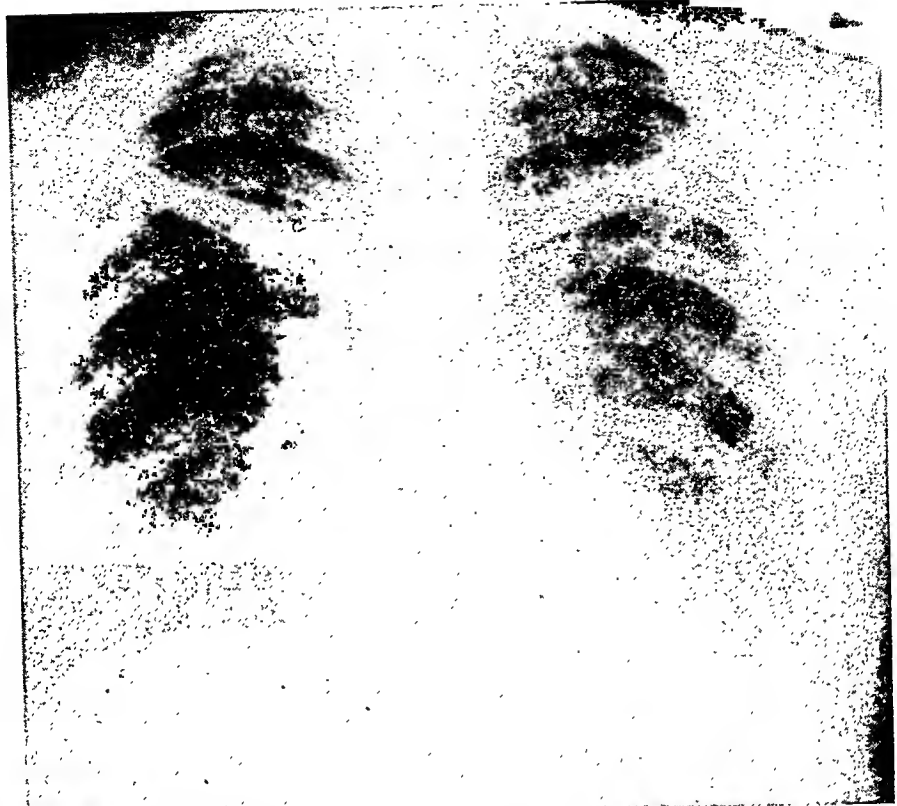


FIG. 1. (*above*) Case M. C., chest roentgenogram on March 29, 1940.
FIG. 2. (*below*) Case M. C., chest roentgenogram on October 19, 1943.

hope of controlling the hemoptyses, but satisfactory paralysis and rise of the diaphragm was not obtained. Chest roentgenograms at this time (figure 2) showed the lesion to be of the same size but denser than in June 1943. In addition a thin aerated crescent now overlay the superior surface of the lesion. During her stay at Undercliff, she was afebrile and asymptomatic except for a dull pain in the region of the left scapula at the time of her hemorrhages. The patient was transferred to the Uncas-on-Thames Sanatorium, Norwich, Connecticut on November 3, 1943 for surgical treatment. Laminography of the left apex showed a rounded, airless mass at the level of the second rib in the 8 and 9 cm. sections. Bronchoscopic examination was negative. No lesions were seen on examination of the oro- and nasopharynx and swabs implanted upon Sabouraud's medium yielded no growth.

In view of the history as well as of the roentgen-ray appearance and behavior of the lesion, it was thought that this was a tuberculous rather than neoplastic lesion. Because the patient was incapacitated by the recurrent hemoptyses, left upper lobectomy was performed on November 26, 1943. The postoperative course was not remarkable. A roentgenogram of January 14, 1944 showed the lower lobe about 60 per cent reexpanded with evidence of thickening of the pleura on the left. She has been in good health at check-ups since then.

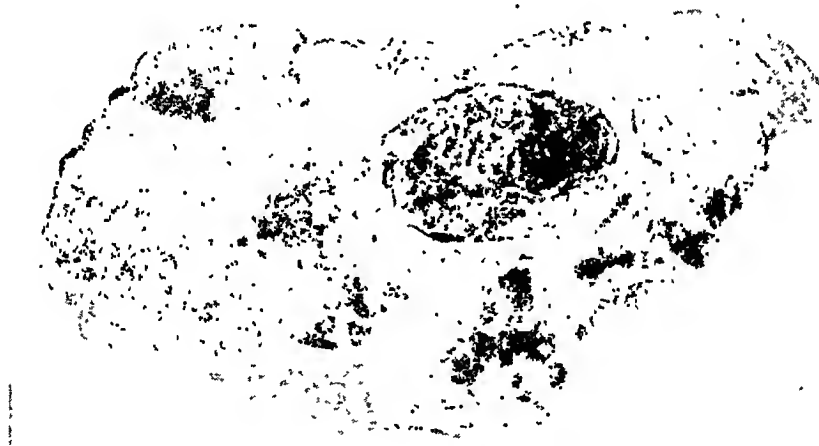


FIG. 3. Case M. C., left upper lobe.

Surgical pathology report: The removed left upper lobe was sectioned in the antero-posterior plane. An oval shaped cavity with a moderately thick fibrous tissue wall was discovered in the center of the parenchyma (figure 3). This cavity was filled by a dark brownish-purple laminated mass not unlike a blood clot. There was a small calcified nodule at the lower pole of the cavity. The remainder of the pulmonary parenchyma appeared uninvolved.

In the microscopic sections, the "cavity" was seen to be a cyst, lying at the end of a dilated bronchus. Bronchial elements (cartilage and smooth muscle fibers) could be identified in the cyst wall. In places there was well preserved columnar epithelium, while non-specific granulation tissue formed other parts of the wall. The contents of the cyst were a dense net of mycelia and spores of a fungus resembling aspergillus (figure 4).^{*} In the surrounding parenchyma were several scattered foci of small round cell infiltration and of diffuse interstitial fibrosis. No tubercles were seen.

^{*} Dr. Morris Tager of the Department of Bacteriology, Yale University was consulted on the mycological aspects of the cases reported. We are indebted for his advice.

Case 2. The second report concerns a 62-year-old white male. He had been a foreman in a machine shop for 37 years but for the last nine years had been a farmer.

In 1944 he entered a local hospital because of severe pain in the right chest. No roentgenograms were taken. White blood count was 10,200, with a normal differential count. Type eight pneumococci were found in the sputum and a diagnosis was then made of right lower lobe pneumonia. His temperature subsided with administration of sulfadiazine, but the drug was stopped on the fifth day when a rash appeared. After three days there was improvement in the skin lesions. He was discharged on the fifteenth day.

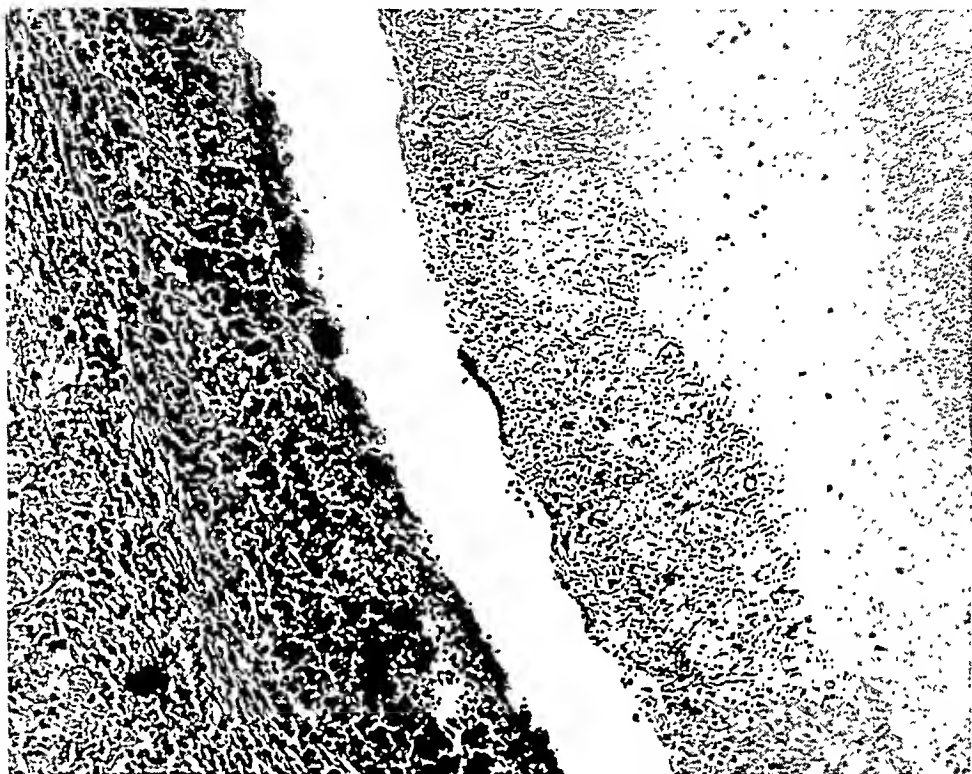


FIG. 4. Case M. C., microscopic section from cyst wall; H & E $\times 166$.

After that time a macular eruption persisted over his body but he paid little attention to it. In August 1945, he expectorated about one dram of bright red blood. A chest roentgen-ray showed infiltration in both hilus areas and extending paravertebrally to the apices. There were also oblique linear densities at the level of the third to the fifth rib on the left as well as emphysema at both bases. He rested in bed for three weeks. Another roentgenogram, one month later, revealed an increase of the infiltration and also an effusion at the right base (figure 5).

The patient was admitted to the Uncas-on-Thames Sanatorium, Norwich, Connecticut on September 6, 1945. He was slightly dyspneic. A macular rash was present over the chest, abdomen and back.

Laboratory data: The red blood cells varied from 2,400,000 to 2,700,000, hemoglobin was 67 per cent, white blood count varied between 625 and 1,800. Differential count showed 32 to 52 per cent lymphocytes and 54 to 68 per cent polymorphonuclears. Serologic tests were negative for syphilis. The urine showed 1+ albumin and an occasional red blood cell but no casts. Since the patient did not expectorate, sputum was not available for examination. Agglutination tests for typhoid, paratyphoid and



FIG. 5. Case A. C., chest roentgenogram on September 4, 1945.



FIG. 6. Case A. C., chest roentgenogram on October 3, 1945.

undulant fever were negative. Blood cultures on the usual media did not yield any growth. Bone marrow obtained by sternal puncture showed aplasia. The patient received liver extract, Betalin complex, penicillin and transfusions.

On October 3, 1945 a roentgenogram (figure 6) showed almost complete clearing of the pleurisy but no other significant change on the right. On the left, however, a dense infiltration with a fuzzy border now radiated out from the hilus toward the base. Two adjacent rounded densities, one of them with a rarefied center, could be seen at the level of the fourth anterior interspace. The patient died on October 7, 1945. An autopsy was performed.

Gross pathology: Numerous reddish-purple, irregularly shaped maculo-papular lesions were seen over the trunk and extremities. These measured 2 to 15 mm. in diameter and slight hyperkeratosis was noted over some of them.

An extensive fibrinous exudate covered the epicardium.

The upper part of the right pleural space was obliterated by fibrous adhesions, while the lower part contained 300 c.c. of cloudy yellow fluid. Several round, well-



FIG. 7. Case A. C., left upper lobe.

defined, slightly raised, grayish-purple and moderately firm areas 8 mm. in diameter were found in the peripheral portions of the right upper and right middle lobe. The lateral segment of the right lower lobe was atelectatic.

The subapical segment of the left upper lobe was attached to the parietal pleura by numerous firm fibrous adhesions. The lung beneath them was bulging and consolidated. The cut surface of this lesion measured 9 cm. Peripherally, it showed a dark-purple cut surface with an occasional grayish pigmented remnant of interlobular septa (figure 7). Some of the alveoli adjacent to this lesion contained a hemorrhagic exudate. The central portion of the lesion was of grayish light-purple color and the outlines of bronchi and vessels were the only pulmonary structures that could be identified. A 1.5 cm. oval shaped cavity, lined by a grayish smooth wall and containing some hemorrhagic exudate, occupied the center of the consolidated area. A group of small abscesses was found in the lateral segment of the left lower lobe and a smaller similar group at the base. Thick pus-like yellow exudate filled their lumina.

Some of the intervening alveoli contained a dark red exudate while elsewhere slight fibrous connective tissue proliferation was noted. Mucopurulent material exuded from all bronchi. The hilar lymph nodes were enlarged. Their cut surfaces bulged and were of grayish purple hue.

The spleen was enlarged, of soft consistency and dark purple color. The Malpighian corpuscles could not be seen. The pancreas, adrenals, liver, gall-bladder and gastrointestinal tract were grossly negative. One enlarged lymph node was found in the mesentery. Its cut surface was yellowish-gray and fairly firm. Both kidneys showed numerous small abscesses containing yellow pus in the cortices and medullae. The pelves were lined by intact mucosa.

Other organs and structures were not remarkable.

Microscopic pathology: In sections from the periphery of the left upper lobe lesion, the alveolar walls were intact and the alveoli contained a fibrino-hemorrhagic exudate. Many of the vessels were occluded by antemortem thrombi with evidence in some instances of organization. Numerous mycelia and small spheroid bodies resembling spores were observed within these thrombi. While some of the mycelia had remained unstained others had absorbed a light-purple to dark-blue stain. Sections from the wall of the larger cavity and surrounding tissue revealed necrosis of the parenchyma with the alveolar shadows filled by an exudate of fibrin and cellular debris. Numerous mycelia, spores, and also fine mycelial filaments ending in a small solid head were seen in the parenchyma and within the lumen of the cavity as well as within the lumina of the vessels. With a Brown-Brenn stain the mycelia and spores appeared light yellow and the filaments gram positive. A van Gieson stain demonstrated splitting and fragmentation of the elastic lamina of the vessels. Mycelia piercing the wall of vessels (figure 8) and spores lying between the elastic lamina could be visualized. Occasional clumps of gram positive cocci were noted in both the preserved and the necrotic parenchyma.

Sections representing the groups of abscesses in the left lower lobe showed areas of caseous necrosis, cellular debris and surrounding hemorrhagic and necrotic alveoli. Numerous arborescent mycelia were seen throughout these lesions. Also present was an oval shaped structure composed of a dark purple center encircled by a concentric ring of pink and then of light purple staining material (figure 9). Under higher magnification, numerous fine radiating lines were seen and this was interpreted as a cross section through the head of a fungus mass.

Sections from other parts of the left and right lung revealed foci of hemorrhagic alveolar exudate. A few alveoli containing cellular debris were usually seen in the center of these lesions whereas at the periphery monocyctic and plasma cell infiltration and an occasional multinucleated giant cell were noted. The muscle fibers of some of the smaller vessels were of pink wax-like appearance and showed loss of nuclei although the endothelium was intact. A perivascular exudate of round and plasma cells was seen. The bronchial walls also contained round and plasma cell infiltration. No microorganisms were discovered in the bronchial lumina.

Numerous small granulomatous lesions observed in the spleen and liver consisted of small spheroid bodies phagocytized by large mononuclear cells.

Sections of the skin revealed hyperkeratosis and vacuolization of some of the deeper epidermal cells. Small foci of plasma and monocyctic infiltration as well as hemorrhages were present in the cutis. Monocytes containing two or three nuclei were seen. Some of the vessel lumina were filled by fine mycelial threads often ending in a small club-shaped head. These structures stained brown in the hematoxylin and eosin preparations.

Sections of the sternal bone marrow showed small infrequent groups of cells of the hematopoietic series, but for the most part complete aplasia of the bone marrow existed.

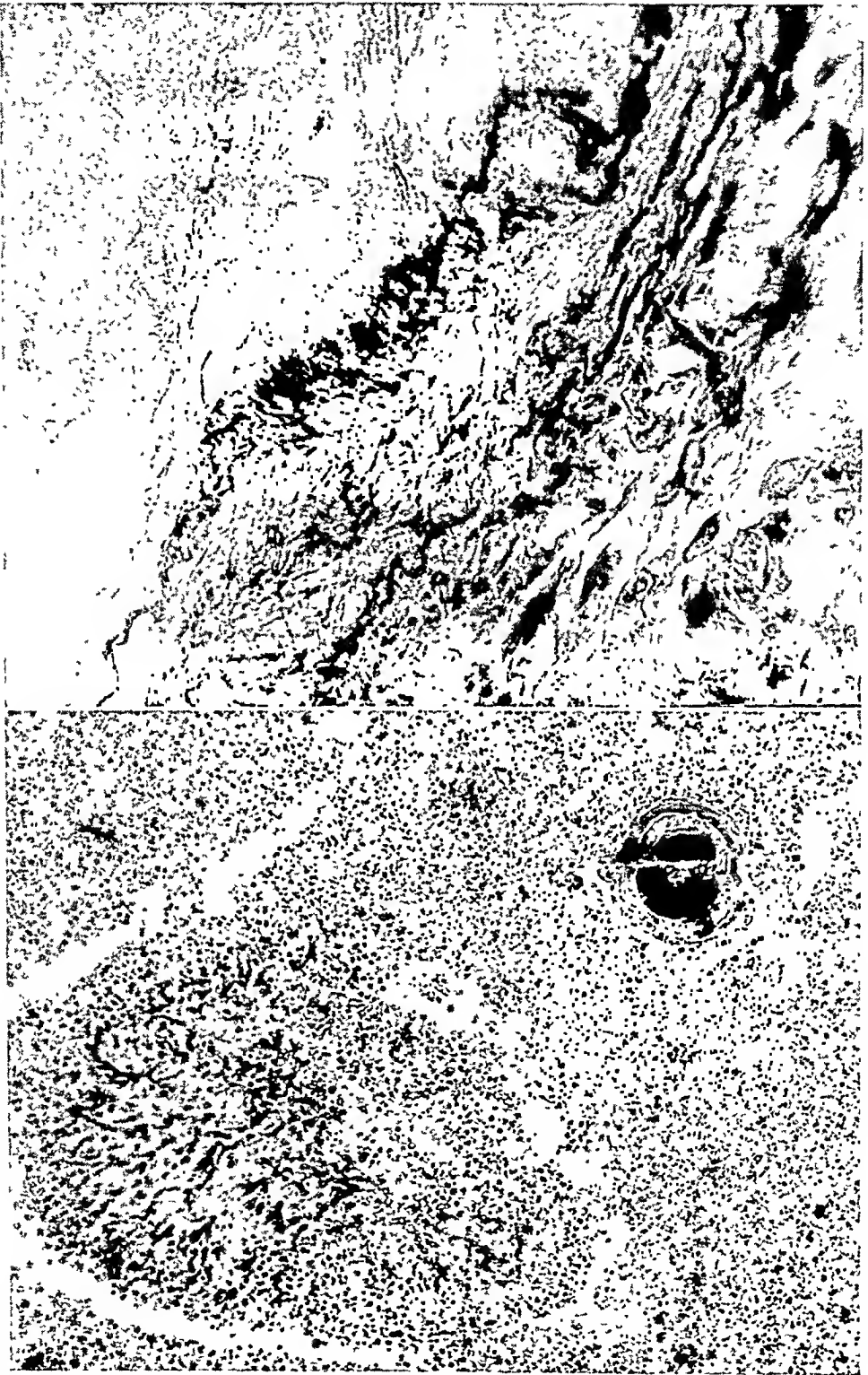


FIG. 8. (*above*) Case A. C., microscopic section from left upper lobe; Elastic-van Gieson stain $\times 360$; note mycelium piercing wall of artery.

FIG. 9. (*below*) Case A. C., microscopic section from left lower lobe; H & E $\times 172$; note mycelia and cross section through head of fungus.

Postmortem bacteriology: Tissue removed from the left upper lobe under sterile precautions was ground with saline and injected into a mouse, a guinea pig and a rabbit. In the mouse, which died four days later, abscesses were found in the mesentery and at the lower surface of the liver. No fungus was found in these lesions. The guinea pig was free of lesions after several weeks. The rabbit, sacrificed on the twenty-ninth day, showed an omental abscess from which *aspergillus* was recovered on culture. Part of the tissue removed at autopsy was implanted on Sabouraud-maltose media and growth of a fungus was obtained in three to four days. Growth at 37° C. was several times more luxuriant than at room temperature. The organism was identified by Dr. Kenneth Raper as *Aspergillus fumigatus Fresenius*.*

Three rabbits were injected intravenously with light saline suspensions of the cultures from the Sabouraud's media. These animals showed labored respiration and paralysis of the hind legs three to four days after injection. In one of them, the white blood count dropped from 10,000 to 4,000 on the second day. The other two rabbits, however, showed no significant changes in their blood count or hemoglobin. Sections of the lungs of these animals revealed numerous small granulomatous lesions. Within some of them capillaries or precapillary vessels contained dark-staining mycelial threads. There was but little necrosis in the lungs. Numerous small foci of necrosis and polymorphonuclear infiltration were noted in the liver and kidneys but microorganisms could not be identified in them. Small myocardial infarcts were also found.

One rabbit was injected intravenously with a Seitz-filtrate of a culture suspension. No significant change in the white blood count occurred.

DISCUSSION

The first of the two cases reported may be interpreted as a bronchiectatic cyst harboring a growth of *aspergillus*. It is remarkable that a fungus growing so well at body temperature showed so little pathogenicity. The mycotic infection did not invade the surrounding parenchyma or vessels and thus cure by surgical procedure was facilitated. The failure of the fungus to migrate into the surrounding tissue and the histology of the cavity wall lead to the assumption that the cavity was preformed and did not result from propagation of the fungus. The inflammatory reaction of the surrounding parenchyma indicates, however, that some interaction between fungus and host took place, and the febrile episodes of this patient may have been related to this.

The interpretation of the roentgenographic changes of the first case was difficult. The early films gave no clue to the existence of a cyst. The well defined oval-shaped lesion found on later examination (figures 1 and 2) suggested bronchial adenoma but the additional parenchymal changes and the small aerated crescent on the upper pole (figure 2) raised doubt as to this interpretation. Cavitation would be reconcilable with tuberculosis, but this diagnosis was undermined by the consistently negative sputum.

After the pathology of the lesion was studied a search of the literature disclosed a report of an almost identical case by Duvé.⁴ This author assumed that the *aspergillus* infection was the primary factor and called the lesion megamycetoma. He pointed to the aerated zone at the upper pole of the lesion as a pathognomonic sign.

Although the pneumonia recorded in the history of the second case offers the possibility that it represented the first manifestation of the terminal disease,

* We wish to express our gratitude to Dr. Kenneth Raper, Northern Regional Research Laboratory, Peoria, Illinois.

the existence of a long standing skin exanthem diagnosed post mortem as mycotic raises the question whether skin or lung served as the primary focus of infection. The presence of lesions in other organs would classify this as a case of systemic aspergillosis.

The roentgen-ray changes of this case differ from what has been described as suggestive of fungus disease of the lung.^{5,6} They resemble the spread and metastases of cancer and were in fact interpreted as such by several roentgenologists. These lesions developed, however, over a period of less than two months and should support a diagnosis of mycosis.

The pathology underlying the roentgen-ray changes is that of a combination of interstitial and parenchymatous type of the disease⁸ plus tissue necrosis hastened by the extensive occlusion of pulmonary vessels. The unrestricted penetration of all pulmonary structures in this second case is in striking contrast to the limited growth of the fungus in the first patient.

Leukopenia, and hypoplasia of the bone marrow have not, to our knowledge, been reported as complications of aspergillosis. It is unlikely that the sulfadiazine administered 18 months earlier would have such a protracted effect. The animal experiments, however, did not give full support to the assumption that this particular strain of aspergillus produces a substance toxic to the bone marrow.

The pulmonary lesions found in the experimental animals correspond to those reported by Lapham,⁸ and the microorganisms were identified histologically. The lesions of liver and kidney were of an acute necrotizing character.

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ELECTROCARDIOGRAPHIC ALTERATIONS RESEMBLING THOSE PRODUCED BY MYOCARDIAL INFARCTION OBSERVED DURING A SPONTANEOUS ATTACK OF ANGINA PECTORIS *

By F. STANLEY RANGLES, M.D., and NATHAN F. FRADKIN, M.D.,
Albany, New York

OCCASIONALLY opportunities have been afforded for securing electrocardiograms of patients with angina pectoris during a spontaneous paroxysm. These

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From the Department of Internal Medicine, Albany Medical College and the Albany Hospital, Albany, New York.

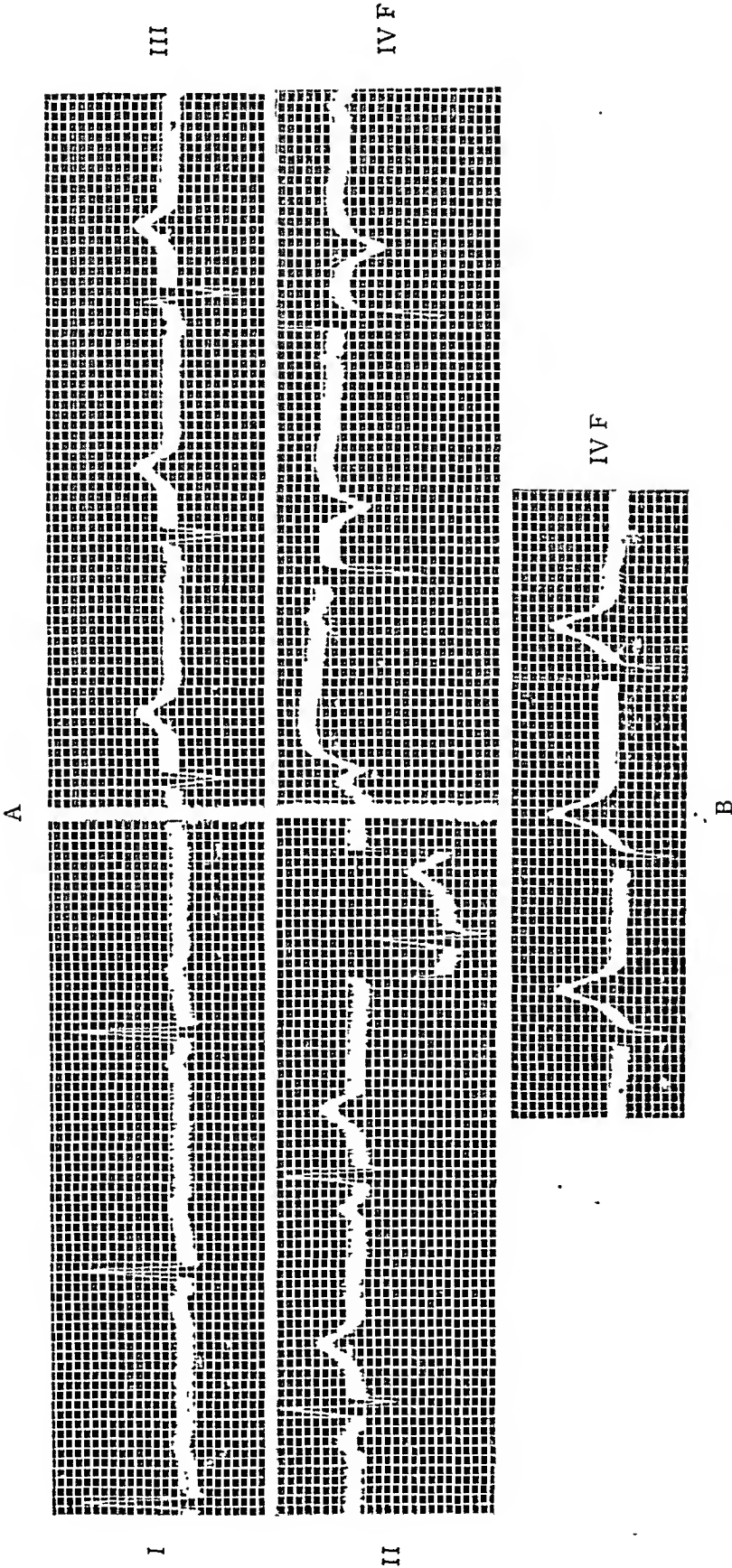


FIG. 1. A. Control electrocardiogram. Tracing taken when patient was free from pain, showing a low T-wave in Lead I and an inverted T-wave in Lead IV. B. Lead IV F taken immediately after relief of substernal distress by nitroglycerine (1/100 gr.). T-wave in Lead IV is now upright.

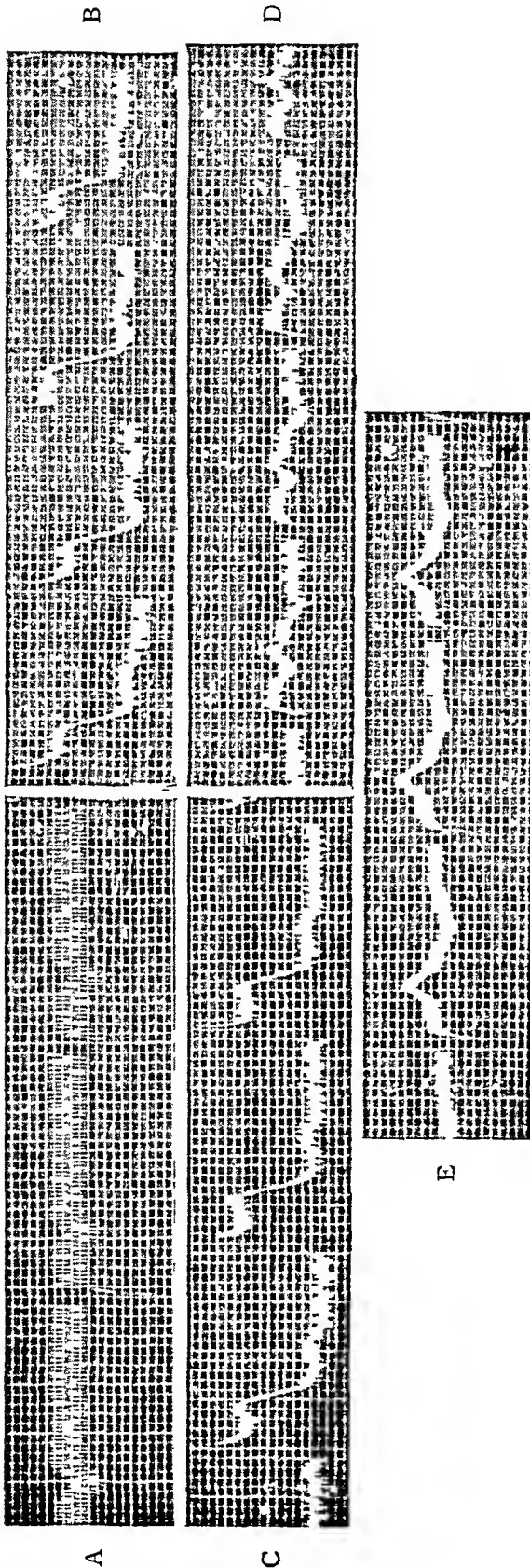


FIG. 2. All tracings in figure 2 are Lead IV F. A. Second record of patient at rest without pain. The T-wave is again inverted. B. About five minutes after A; patient had severe attack of subacute pain which occurred spontaneously. Striking elevation of the ST interval. C. One minute after patient received nitroglycerine (gr. 1/100) under tongue. No relief from pain and no change in ST segment. D. Thirty seconds after a second nitroglycerine tablet. Pain subsiding. Slight elevation of ST segment and partial inversion of T-wave. E. Two minutes after D. Pain completely relieved. Record now essentially normal and similar to figure 1B.

have shown distinct changes resembling those found after thrombosis of a large coronary artery.¹ We should like to place on record our electrocardiographic findings in a patient observed before, during, and after a spontaneous attack of angina pectoris.

CASE REPORT

Mr. F. Van V., aged 46, was seen in the office by one of us (F. S. R.) on January 3, 1944, complaining of substernal distress on exertion. A brief history was obtained, an electrocardiogram was taken, and an appointment was made for a more complete examination three days later. This record showed left axis deviation, a low T-wave in Lead I and an inverted T-wave in Lead IV (figure 1A).

He returned three days later and a more detailed history was obtained. He stated that he had experienced severe substernal pain after doing heavy work, hurrying up stairs, etc. for the preceding four months. The pain had been so severe that he had been forced to stop and rest, whereupon the distress would gradually subside. For the past three weeks he had had similar attacks of pain at rest. On several occasions he was awakened from his sleep with severe angina. Excitement or nervous tension often precipitated attacks.

Physical examination was essentially negative. Blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. Blood Wassermann test was negative. Urinalysis was negative. During the examination, he had an attack of substernal pain. It was apparently severe, and the heart suddenly became rapid and irregular (coupled rhythm). Fearing serious developments the patient was given one 1/100 grain nitroglycerine tablet under his tongue. Within a minute the pain began to subside and the cardiac irregularity disappeared. A fourth lead electrocardiogram was taken within five minutes after the pain subsided (figure 1B).

The patient was again seen in the office eight days later. He had had attacks nearly every day, several without exertion. All had been promptly relieved by nitroglycerine. Because of the marked change of the T-wave in Lead IV noted on the previous visit, Lead IV F was repeated before the patient was interviewed or examined. Unfortunately the record was disturbed by alternating current due to a faulty ground connection, but the general form was the same as in the original record, the T-wave being inverted (figure 2A).

During the examination about five minutes later he complained of severe chest pain. He was immediately returned to the electrocardiograph room and Lead IV F was again taken, showing the striking change seen in figure 2B. A 1/100 grain nitroglycerine tablet was dissolved under the patient's tongue. After one minute he obtained no appreciable relief, and another record was taken showing very little change (figure 2C). A second tablet of nitroglycerine was given and within 30 seconds the patient showed and expressed marked relief. Another record taken shows striking change in the level of the ST segment (figure 2D). After a two minute interval the pain had entirely gone, and a final record at this time showed return of the T-wave to the upright form (figure 2E).

On January 28 the patient was again seen in the office, and had another attack of severe chest pain. This time the three standard leads of the electrocardiogram were taken during the attack, and after relief was obtained by nitroglycerine. Figure 3A is the record taken during the attack and figure 3B two minutes later when the pain had completely subsided. While there are definite changes in the T-waves, in Leads I and III, these are much less striking than those previously observed in Lead IV. No disturbance in rhythm was ever detected except during the first attack on January 6.

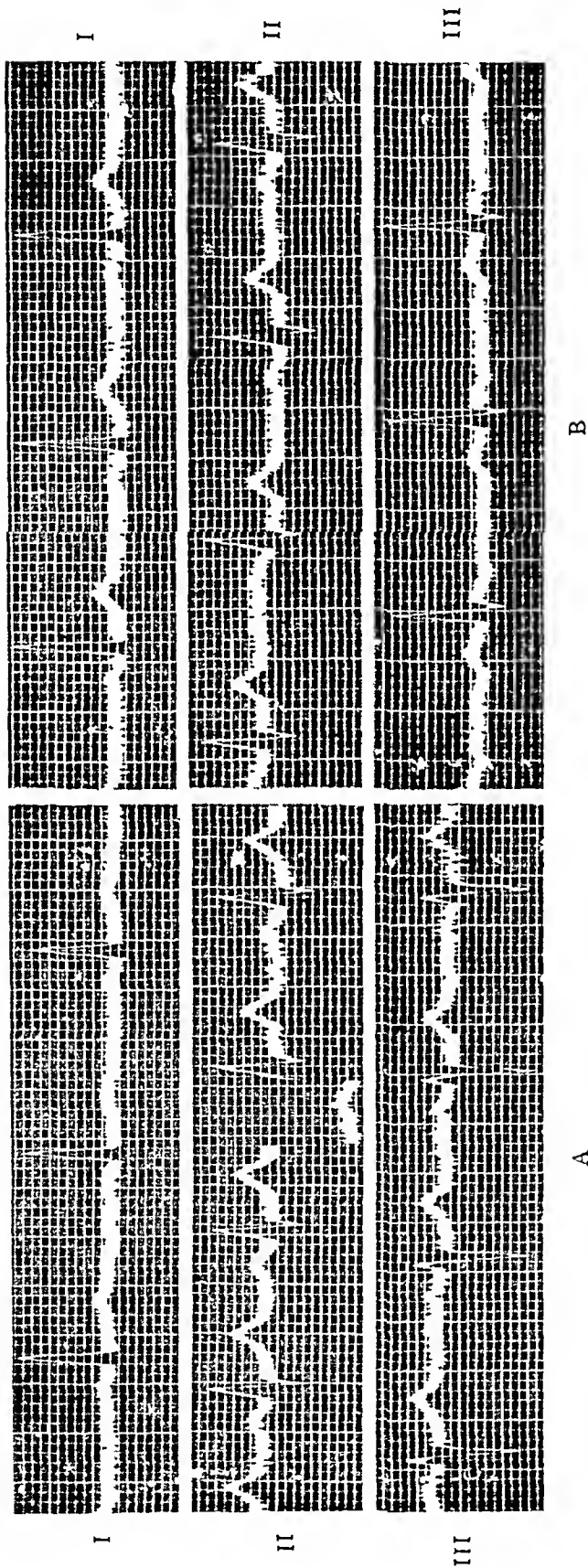


FIG. 3. Three standard leads. *A*. During another severe spontaneous attack of angina. T_1 low and T_3 upright. *B*. Two minutes after complete relief of pain from nitroglycerine (gr. 1/100). T_1 higher and T_3 mainly inverted.

COMMENT

The electrocardiographic changes recorded in this patient during an attack of angina pectoris are similar to those observed after occlusion of a large coronary artery, and indicate a profound disturbance in the coronary circulation. These findings would support the opinion that anginal attacks are caused by myocardial ischemia. Opinions have differed regarding the pathogenesis of the myocardial ischemia. Some believe it to be due to an increase in the work of the heart, while others believe that it is brought about by an alteration in the caliber of the affected coronary artery (coronary spasm). Our observations would support the latter theory, inasmuch as the profound electrocardiographic changes appeared and disappeared while the patient was at rest and with no significant increase in the heart rate.

SUMMARY

Electrocardiographic changes resembling those observed after a myocardial infarction are presented from a patient during a spontaneous attack of angina pectoris.

A diminution in the caliber of the affected coronary artery rather than an increase in the work of the heart is suggested as the probable pathogenesis of the myocardial ischemia.

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BARBITURATE POISONING: COMBINED USE OF RESPIRATOR, FLUID, CENTRAL NERVOUS SYSTEM STIMULANTS AND PRESSOR AGENTS*

By DAVID T. DRESDALE, M.D., HURLEY L. MOTLEY, M.D., JOHN R. WEST, M.D.,
and JAMES K. ALEXANDER, M.D., *New York, N. Y.*

THIS case is presented to demonstrate the use of a respirator, combined with parenteral fluids, central nervous system stimulants and pressor agents, in sustaining life for three days in a patient deeply comatose from barbiturate poisoning.

The patient was a 63 year old hypertensive and diabetic white woman, with suicidal tendencies, who had taken, as well as could be determined, approximately 2 gm. of Sodium Seconal and 0.6 gm. of Sodium Amytal, eight to ten hours before admission

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From the Department of Medicine, Columbia University, College of Physicians and Surgeons; and the First Medical Division and Chest Service, Bellevue Hospital, New York, N. Y.

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to the emergency ward at Bellevue Hospital. At the time of admission the patient was deeply cyanotic, unresponsive to stimuli, a-reflexic and almost pulseless. The blood pressure was unobtainable. Respiratory movements consisted of a shallow gasp occurring every one to two minutes. She was described as having been in the above condition for at least one hour before being brought to the hospital. After an intravenous injection of epinephrine hydrochloride (0.5 mg) was given, the blood pressure became obtainable and the pulse palpable. Oxygen (100 per cent) at the rate of 10 liters per minute was administered by means of an OEM (Oxygen Equipment Mask) and artificial respiration was started at once employing the "squeeze the chest" method. Although the blood pressure could be maintained erratically by intravenous epinephrine every three to four minutes, she remained apneic and deeply cyanotic. This method of artificial respiration has been found to ventilate the lungs on an average less than one liter per minute in similar subjects.¹

In view of the inadequate ventilation, the Pneumatic Balance Respirator, "Burns Model," hereafter referred to as the PBR, was applied

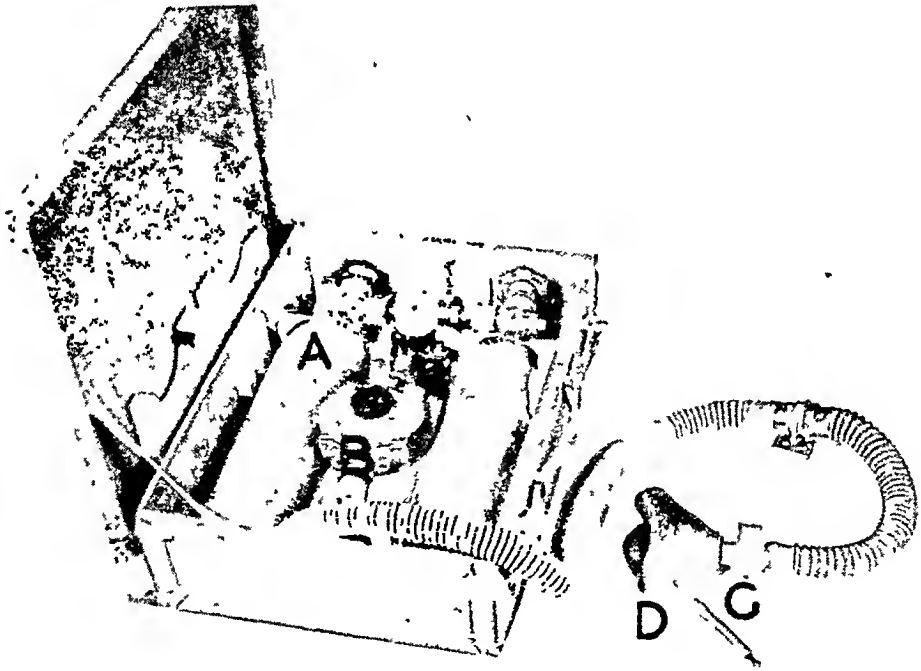


FIG. 1. The PBR Respirator Unit (A) High pressure oxygen cylinder. (B) Pressure demand regulator. (C) PBR (Pneumatic Balance Respirator, "Burns Model"). (D) Mask.

The PBR is a small and compact device (figure 1), developed by the Army Air Force,^{1,2} for giving artificial respiration by converting continuous positive pressure into intermittent positive pressure.

The entire artificial respiration apparatus consists of (a) a high pressure oxygen tank; (b) a pressure demand regulator, of the type used by the Army Air Force, which supplies oxygen on inspiratory "demand" from the tank, and in addition a continuous pressure ("line pressure"), which may be varied by

adjustment of the regulator, from 12 cm. of water up to 30 cm. of water; (c) the PBR; (d) anesthesia mask, or in deep coma cases such as this one, an intratracheal tube; (e) connecting tubing.

The operation of the Pneumatic Balance Respirator (PBR) is such that it allows the compressed gas to pass from the pressure demand regulator to the patient (positive pressure inspiration), until the inspiratory pressure reaches about 75 per cent of the "line pressure," at which point the inspiratory valve of the PBR closes and expiration then takes place passively, expired air passing out through small ports in the side of the PBR. As expiration is completed, the inspiratory valve re-opens and the compressed gas flows again from the high pressure cylinder through the regulator and the PBR to the patient.

A clearing of the cyanosis was noted almost immediately after the PBR was applied, using an endotracheal tube and a line pressure of 16 cm. water with 100 per cent oxygen. One half hour later spontaneous respiratory movements were restored, but the PBR was continued because respirations were shallow and cyanosis returned upon removal of the respirator. The oxygen saturation of the arterial blood with the PBR seven hours later was 102 per cent and the pH was 7.37. This finding gave proof that ventilation was adequate although the actual ventilatory volume was not measured. In other apneic subjects the pulmonary ventilation with the PBR cycling properly on a line pressure of 16 cm. of water, has been found to vary from 6 to 10 liters per minute.¹

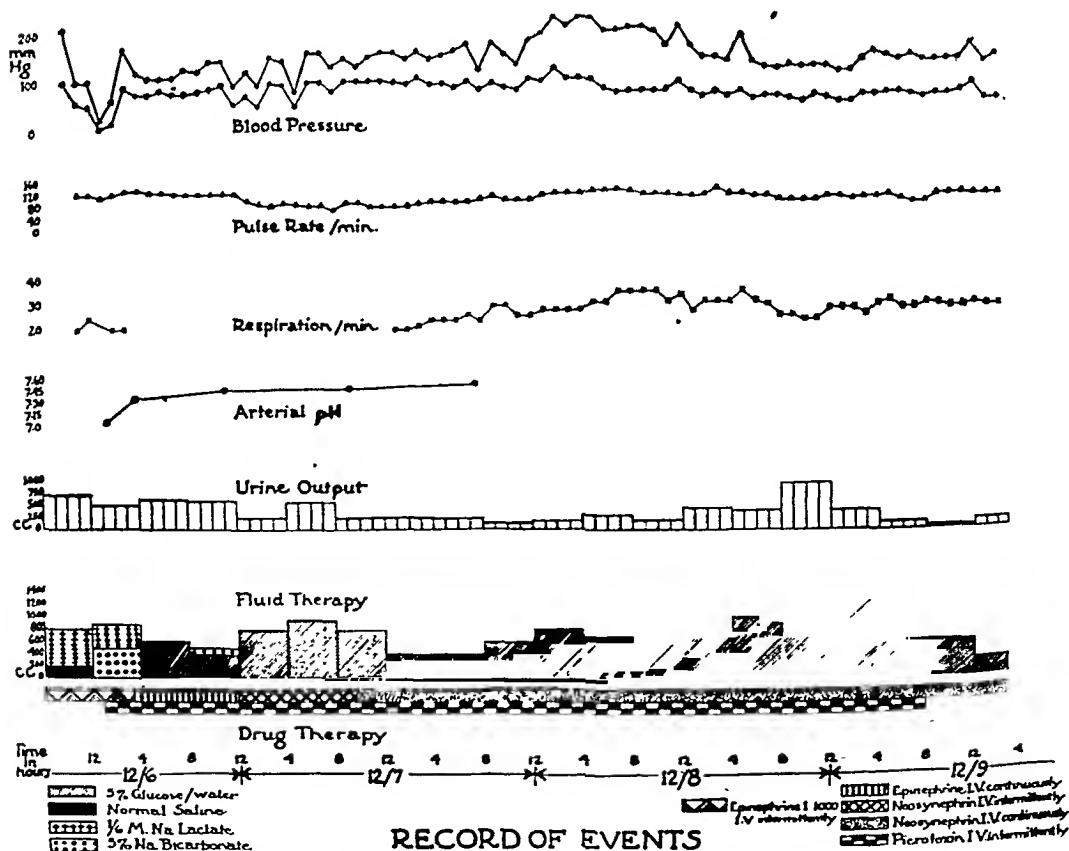


FIG. 2.

After an initial period of about one and a half hours on the PBR, the respirator was removed so that the stomach could be washed out. Bubbling râles were heard in both lungs after the gastric lavage; it was suspected that some fluid may have been aspirated. These râles cleared shortly after the PBR was reapplied and the lungs remained relatively clear of moisture during the remainder of the time (76 hours) that the respirator was used. The clearing of moisture in lungs with the PBR has been observed in other coma cases.^{1, 3}

The arterial blood pressure was maintained throughout the 78 hours by means of the sympathomimetic drugs, epinephrine and neosynephrine. During the first eight hours epinephrine in 0.5 mg. doses was given intravenously at intervals with wide fluctuation of the blood pressure and rapid pulse rate. During the next eight hours the blood pressure was maintained at a more or less constant level (average 130/80) by regulating the inflow of infusion fluids containing epinephrine, 8 mg. per liter. However, the tachycardia persisted.

Neosynephrin was substituted for epinephrine 16 hours after admission. A total of 900 mg. of neosynephrin was given during the next 62 hours (figure 2). It was given at first in doses of 0.3 mg. intravenously, intermittently, and the blood pressure was sustained with a slower heart rate. Neosynephrin was then added to the infusion fluid, 100 to 200 mg. per liter, and by controlling the rate of flow of the infusions the blood pressure was maintained for the following 52 hours at the desired level (average 160/90 mm. Hg) with a much slower pulse rate than with the epinephrine (figure 3). An exception to this was noted for a period of time when picrotoxin seemed to have its maximum effect.

Keys and Violante,⁴ in man, and Landis and Geiter,⁵ in dogs, have shown that neosynephrin will elevate and maintain blood pressure without an undesirable accompanying tachycardia. Because of this property neosynephrin has been described as the pressor drug of choice in surgical shock⁶ and anesthesia.^{7, 8} Since the case described here, we have had the opportunity to observe the use of neosynephrin administered intravenously with infusion in six coma cases with complete apnea and vasomotor collapse. In each case the blood pressure was restored and maintained with a normal pulse rate.

It might be noted that injections of caffeine sodium benzoate in doses of 0.5 gm., intravenously, or benzedrine sulfate in doses of 10 mg., intravenously, concomitant with the epinephrine did not appear to have any appreciable effects and were discontinued early.

In an effort to stimulate the central nervous system, repeated doses of picrotoxin totalling 940 mg. were given intravenously over a 67 hour period. The doses varied from 10 mg. every 20 to 40 minutes during the first day to 20 mg. every 30 to 60 minutes during the next two days. Shortly after picrotoxin was started the time interval between injections of epinephrine necessary to maintain the blood pressure was considerably lengthened, the respiratory rate was increased, the corneal reflex (used as a guide for the administration of picrotoxin) became active and was maintained for the greater part of the time, and the patient gagged several times on the intubation tube. The deep tendon reflexes never became active.

The patient was in severe acidosis at the time of admission. A blood arterial pH taken several hours after starting the PBR and after 960 c.c. of 1/6 M. Na lactate had been given intravenously was 7.09. Three hours later and after 500 c.c. of 5 per cent Na bicarbonate had been given intravenously the arterial pH was 7.37. Thereafter the pH was kept within normal limits or slightly on the alkaline side. This was accomplished by the combined use of alkaline, normal saline and glucose and water infusions, adequate pulmonary ventilation with sufficient removal of the CO₂ and the

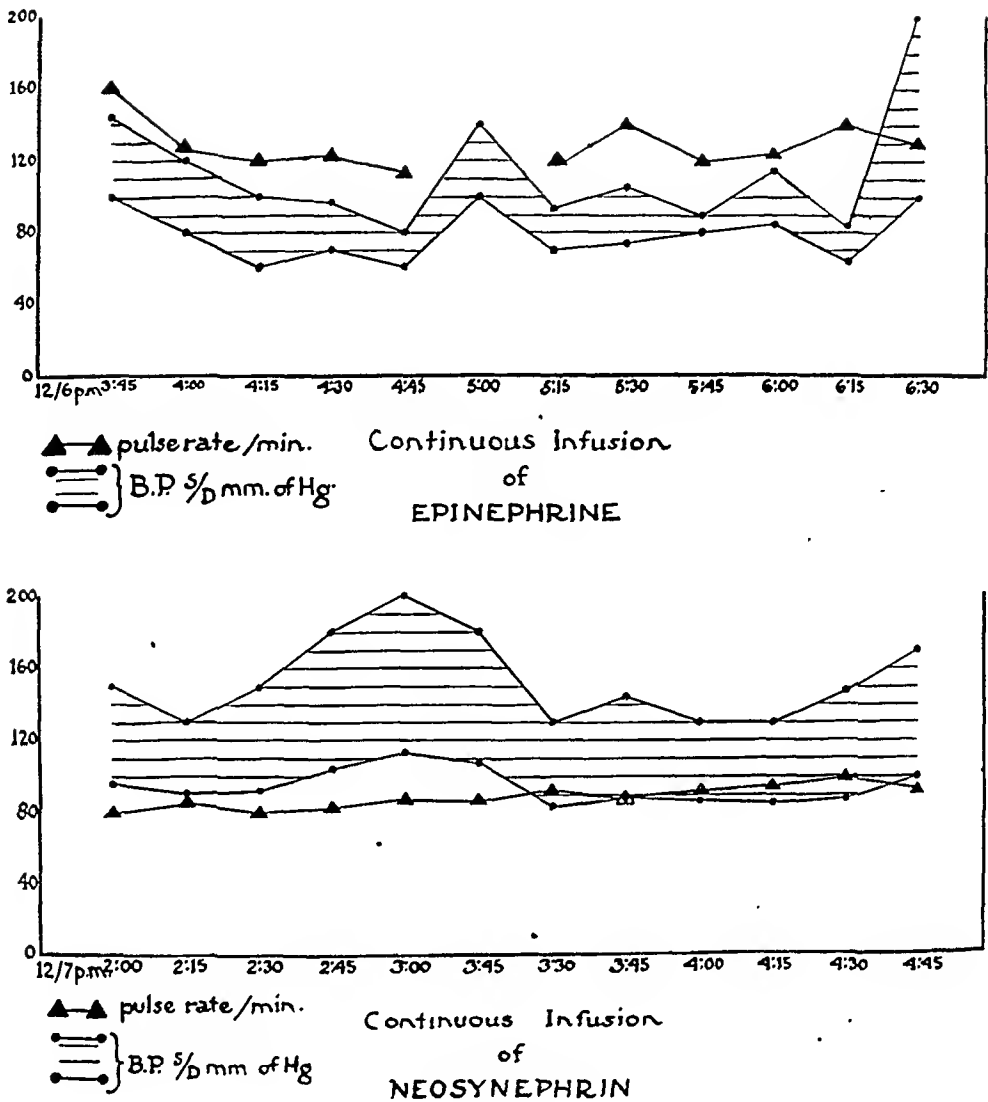


FIG. 3.

maintenance of good renal function. The latter was probably related to an adequate mean arterial pressure maintained throughout most of the 78 hours.

A total of 13,510 c.c. of fluids, containing 11 gm. of Na, was administered over the 78 hour period and during this time 7480 c.c. of urine were excreted (figure 2). The hematocrit taken on the second day was normal (49 per cent). All glucose given was covered by insulin.

The patient never recovered consciousness, having apparently suffered irreversible central nervous system changes. This was probably brought about by the prolonged period of anoxia and extreme acidosis prior to treatment. At the end of 78 hours the respirator was removed and the patient was tested breathing air spontaneously. For eight minutes she continued regular shallow respirations with no cyanosis, then suddenly stopped breathing. An autopsy was not performed. The patient was signed out by the medical examiner as barbiturate poisoning on the basis of clinical findings and urine and gastric contents positive for barbiturates.

In concluding, we believe this case illustrates how the combined and judicious use of a respirator, alkalis, fluids, central nervous system stimulant and pressor

drugs can cope with the manifold problems presented by an unconscious subject with the possibility of maintaining life for long periods, thus favoring a better chance of a successful recovery.*

The authors desire to express their appreciation for the helpful suggestions and advice given by Dr. Dickinson W. Richards, Jr., Director of First Medical Division, Bellevue Hospital, and for the coöperation of the members of the First Medical Division house staff.

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* More recently, a similar type of patient with barbiturate poisoning who was deeply comatose, apneic, cyanotic, and pulseless on admission, was treated in a similar manner. The PBR was removed after 24 hours at which time spontaneous respirations were adequate for maintaining normal respiratory gas exchange. This patient regained consciousness two days after admission and made an uneventful recovery.

EDITORIAL

BCG VACCINE

THE factors which determine immunity from tuberculosis differ substantially from those which are operative in the case of many other infections. Humoral antibodies appear to play at most a minor rôle, and resistance depends primarily upon an altered reactivity of the tissue cells. Although some degree of immunity may be produced in animal experiments by the inoculation of killed organisms, any notable degree of protection depends upon the presence of living tubercle bacilli in the body. All practicable methods of immunization are based upon the observation—which has been confirmed by innumerable experiments—that inoculation of animals with a strain of tubercle bacilli of low virulence may delay or prevent the development of a progressive generalized infection if the animal is subsequently inoculated with a virulent strain. Such an immunizing infection is regularly accompanied by a hypersensitiveness to tuberculin, and a tuberculin test is the most practicable way of determining its presence. It is probable, however, that hypersensitiveness to tuberculin is not an essential and perhaps not even a useful manifestation of the immunity reaction.

Although the incidence of tuberculosis has been substantially reduced by the measures currently employed, it is still all too prevalent and continues to be a major health problem. A safe and reasonably effective method of increasing resistance by vaccination would be an important supplement to these measures. It would be particularly valuable in the case of infants and also of young adults such as nurses and medical students who are unusually exposed to infection because of an unfavorable environment or occupational hazards. To be useful, however, vaccination must be carried out before infection is naturally acquired—while the tuberculin reaction is still negative—and it must antedate infection by a sufficient interval to permit the development of immunity, preferably at least one month. There is no evidence that vaccination alters the course of an established infection. The rationale of the procedure is sound. It should be safer for the individual deliberately to establish a primary infection with a strain of low virulence than to await almost inevitable infection under natural conditions with a strain of unpredictable but certainly of higher virulence.

BCG (bacillus of Calmette and Guérin) is a bovine strain of tubercle bacillus which was isolated in 1906 from the milk of a tuberculous cow. This was cultivated in Calmette's laboratory in the Pasteur Institute in Paris on media which were regarded as unfavorable for the maintenance of virulence. After 13 years' cultivation its virulence had become so attenuated that it caused only localized nodular lesions in guinea-pigs and did not give rise to a generalized infection. It still produced tuberculin in cultures, however, and animals which had been inoculated with it showed a significant degree of

protection against subsequent injections of virulent strains of tubercle bacilli.

On the basis of these observations Weil-Hallé and Turpin (1921) began the immunization of infants, at first administering the vaccine by mouth. As this resulted in only a small proportion of "takes" as indicated by the development of a positive tuberculin reaction, they changed (1924) to subcutaneous injections. After the safety of the procedure appeared to be established, it was used on an increasing scale in continental Europe where, it has been estimated, the vaccine has been administered to over 5,000,000 individuals. It has also been used fairly extensively in South America. In the United States, however, it has been used only to a very limited extent because of skepticism both as to its safety and its effectiveness.

Vaccination fell into temporary disrepute in Europe following the death in Luebeck, Germany, in 1930 of 77 vaccinated infants from progressive tuberculosis. Later, however, this was proved to be the result of a laboratory error in which a virulent strain of tubercle bacilli was substituted for BCG. In this country, doubt as to its safety has been based rather on the theoretical possibility that the culture might still contain some virulent organisms or that it might unexpectedly regain some measure of its original virulence while under cultivation. This view received some support from a report of Petroff et al.¹ that they had succeeded in dissociating their BCG culture into rough and smooth colonies and that strains derived from the latter at times were capable of producing progressive disease in animals. Many more recent attempts to confirm these observations with other strains of BCG have uniformly failed. No one has been able to prove that progressive disease in human beings has ever followed the use of the vaccine, and its safety in this respect is now generally acknowledged.²

Subcutaneous injections of BCG were often followed by troublesome local reactions consisting of necrosis and ulceration which might take several weeks to heal. Necrosis and sloughing of the regional lymph nodes were also frequent and often left unsightly scars. This difficulty was reduced by the substitution of intracutaneous for subcutaneous injections by Wallgren,³ and it has been practically eliminated by the multiple puncture method of Rosenthal.⁴ A few drops of a culture suspension of suitable density are placed on the sterilized skin of the arm, and with a sharp needle multiple skin punctures are made through the vaccine just as is customarily done in vaccination against smallpox except that the punctures are made somewhat more deeply and are more widely spaced. This results in the development of a small nodule at the site of each puncture which may attain a diameter of 3 to 6 mm.

¹ PETROFF, S. A., BRANCH, A., and STEENKEN, W., JR.: Study of *Bacillus-Calmette-Guerin* (BCG): Biological characteristics, cultural "dissociation" and animal experimentation, *Am. Rev. Tuberc.*, 1929, xix, 9-46.

² Report of a conference on BCG vaccination, *Pub. Health Rep.*, 1947, lxii, 346-350.

³ WALLGREN, A.: Intradermal vaccinations with BCG virus: preliminary note, *Jr. Am. Med. Assoc.*, 1928, xci, 1876-1881.

⁴ ROSENTHAL, S. R.: The multiple puncture method of BCG vaccination, *Am. Rev. Tuberc.*, 1939, xxxix, 128-134.

and which subsides after about a month without causing discomfort, necrosis at the site of the vaccination or in the regional lymph nodes, or appreciable scarring. The effectiveness of the vaccination in inducing a mild infection is indicated by the development of a positive tuberculin reaction in over 99 per cent of the cases.⁵

The practicability of the procedure has been confirmed by many other investigators, among these Birkhaug.⁶ He carried out a careful study in guinea-pigs and showed that if an adequate number of punctures (30 to 60) were made, the animals developed a substantial degree of resistance to subsequent infection with a virulent culture. This was at least equal to if not greater than that induced by scarification or intracutaneous injection. He subsequently used the method in vaccinating over 3000 human beings with no untoward results except minute local abscesses in 3.8 per cent of the subjects, which were not troublesome and which healed promptly. Of 1500 subjects so vaccinated, 98 per cent gave a positive tuberculin reaction two months later.

In spite of the large number of individuals who have been vaccinated and the long period of observation since vaccination was begun, it is far more difficult to reach any valid conclusion as to its effectiveness in reducing the morbidity and mortality from tuberculosis. Rosenthal⁵ has collected and summarized many of the reported studies, chiefly from European countries. These appear to show a reduction in mortality among the vaccinated to a figure from one-third to one-fifth of that in the controls. In brief, however, these figures are not convincing because in few if any of the series do the "controls" constitute a group which is strictly parallel and comparable with the vaccinated.

The need for adequately controlled studies has been fully appreciated in this country, and a few have now progressed to a point which permits some conclusions to be drawn. Several studies have been made among nursing personnel and medical students. Although these are limited in the numbers studied and not so strictly controlled as is necessary for a crucial test, they are in harmony in showing a reduction of infection among the vaccinated. Thus Ferguson⁷ reported that 0.825 per cent of 1005 nurses, vaccinated intracutaneously, in eight Saskatchewan general hospitals developed manifest tuberculosis during a period of 2.5 years, as compared with 3.82 per cent among 759 nonvaccinated individuals with originally negative tuberculin reactions. In three tuberculosis sanatoria the corresponding figures during a period of observation of about a year were 2.46 per cent for the 203 vaccinated and 15.9 per cent in 113 nonvaccinated individuals. The lesions in

⁵ ROSENTHAL, S. R., BLAHD, M., and LESLIE, E. I.: Ten years' experience with BCG (experimental and clinical), *Jr. Pediat.*, 1945, xxvi, 470-480.

⁶ BIRKHAUG, K.: Protective value of the intracutaneous and percutaneous methods of BCG vaccination (comparative experimental investigation), *Acta med. Scandinav.*, 1944, cxvii, 274-312.

⁷ FERGUSON, R. G.: BCG vaccination in hospitals and sanatoria of Saskatchewan, *Canad. Jr. Pub. Health*, 1946, xxxvii, 435-451.

those who developed the disease were less extensive in the vaccinated group. Rosenthal⁸ has reported similar results.

Of the studies in North America carried out on the general population, three will be summarized. Baudouin⁹ has reported a study based on the vaccination of over 20,000 infants in Canada and observed over a period of 11 years. Restricting his report to children who were exposed to open cases of tuberculosis in their homes, he found that the mortality from tuberculosis in 793 vaccinated cases was about 70 per cent less and the morbidity 47 per cent less than in 1239 controls so exposed. In his series the resistance seemed to be maintained throughout the period of observation of seven years.

Aronson et al.¹⁰ reported an extensive study carried out on Indians from one to 20 years of age, living on four reservations in the United States and in 12 communities in Alaska. The economic level of the group was low, and there was a high degree of exposure to tuberculosis. There were 1550 (intracutaneously) vaccinated individuals and a satisfactory control group of 1457 with negative tuberculin reactions who were not vaccinated. These were followed for six years or more, by means of repeated physical examinations, roentgenograms and tuberculin tests. The mortality was 4 among the vaccinated, all starting during the first two years, as compared with 28 among the controls, which were fairly evenly distributed over the six year period. The number showing manifest disease was 40 among the vaccinated, 4.7 per 1000 person-years, and 185, or 24.3 per 1000 person-years, in the controls. The latter were evenly distributed over the six year period, but the rate among the vaccinated fell progressively from 11.8 during the first year to less than 1 per 1000 person-years during the sixth year. This suggested that the degree of protection increased rather than decreased during this period under the conditions obtaining in this group.

The most extensive carefully controlled study is that of Rosenthal et al. carried out in newborn infants in Chicago; among a low income group in which there was a relatively high degree of exposure to tuberculosis. The infants were largely those delivered at the Cook County Hospital. The families were examined, and if there was a case of demonstrable tuberculosis in another member of the household, the infant was isolated for from six to 12 weeks before being returned to the home. Infants in the control series, subject to such exposure, were similarly isolated. The results of the first seven years' observation were reported in 1945,⁵ and a later report covering the same group has recently been published.¹¹ Of the children not directly

⁸ ROSENTHAL, S. R.: The use of BCG vaccination among medical and nursing students, *Hospitals*, 1943, xvii, April, 75-78.

⁹ BAUDOUIN, J. A.: Vaccination against tuberculosis with BCG vaccine, *Canad. Jr. Pub. Health*, 1940, xxxi, 362-366.

¹⁰ ARONSON, J. D., and PALMER, C. E.: Experience with BCG vaccine in the control of tuberculosis among North American Indians, *Pub. Health Rep.*, 1946, lxi, 802-820.

¹¹ ROSENTHAL, S. R., LESLIE, E. I., and LOEWINSON, E.: BCG vaccination in all age groups. Methods and results of a strictly controlled study, *Jr. Am. Med. Assoc.*, 1948, cxxxvi, 73-79.

exposed to tuberculosis in the household, among 1417 vaccinated by the multiple puncture method there were 11 cases of demonstrable tuberculosis as compared with 39 cases among 1414 controls, giving morbidity rates per 1000 person-years of 1.95 and 6.46 respectively. There was one death from tuberculosis in the vaccinated and seven in the control group. Of the children directly exposed to tuberculosis in the household there were two cases of tuberculosis (with no deaths) in 151 vaccinated children, whereas in the control group of 105 there were five cases with four deaths, giving morbidity rates of 3.86 and 17.60 per 1000 person-years. As the control groups in this study were adequate, the figures must be regarded as significant.

The interest aroused by these observations resulted in a conference of those actively engaged in this work, which was held Sept. 7, 1946, under the auspices of the United States Public Health Service.² It was recommended that BCG vaccine not be made available commercially at present but that extensive investigations be carried out coöperatively with recognized research groups, especially in population groups highly exposed to tuberculous infection. The Tice Laboratory in Chicago has been designated as a central laboratory for preparation of the vaccine for such studies.

To determine with any precision how much protection is afforded, how long it lasts, and what plan of vaccination will best produce and maintain this will require a great deal more work and protracted observation, probably for at least two decades. For the present, one may conclude that BCG vaccine is safe and that it need not cause troublesome local reactions if properly administered. It also appears to give a significant degree of protection throughout the relatively limited periods (about six years) during which the vaccinated groups have been observed. It seems possible that this may be prolonged or restored by revaccination if the tuberculin reaction becomes negative, as has been Rosenthal's practice in his group.

As with any type of vaccination, the immunity produced by BCG is only relative, and if the degree of exposure (size of the inoculum) is great enough or probably if the virulence of the infecting strain is sufficiently high, the immunity may be overcome and progressive disease develop. In heavily exposed groups, at least, BCG promises to be a valuable addition to the preventive measures now generally employed but not a substitute for them. If these preliminary conclusions are confirmed by the work now in progress, we may hope that the vaccine will soon be available for use on a more extensive scale.

P. W. C.

REVIEWS

The Chemical Kinetics of the Bacterial Cell. By C. N. HINSHELWOOD, F.R.S. x + 284 pages; 16 × 24.5 cm. Oxford University Press, New York. 1947. Price, \$6.75.

The writer has posed in this volume the interesting problem of the principles of applicability of chemistry and physics to the living bacterial cell. Using the Langmuir isotherm and other physicochemical relationships, the writer applies these to the metabolism of the living bacterial cell.

Of special interest to the physician is the problem of adaptation of bacteria to drugs. Upon this phenomenon the development of drug fastness probably depends. The writer also develops in a mathematical manner the phenomenon of lag concentration graphs, of bacteria in normal media and in the presence of familiar anti-infective drugs.

The problem of bacterial variants is discussed from a physicochemical standpoint with regard to their environment and the action of drugs.

The death rate of bacteria is discussed from a mathematical viewpoint. The author closes the book with an excellent discussion of the second law of thermodynamics in relation to living cells, and challenges the reader with long-range and short-range problems regarding the characteristics of living matter.

The book is well written and mentally stimulating.

J. C. K., JR.

Congenital Malformations of the Heart. By HELEN B. TAUSSIG, M.D., Associate Professor of Pediatrics, The Johns Hopkins University School of Medicine, and Director of the Children's Cardiac Clinic of the Harriet Lane Home of The Johns Hopkins Hospital. 618 pages; 18 × 26 cm. The Commonwealth Fund, 41 East 57th St., New York. 1947. Price, \$10.00.

This volume is a valuable addition to the literature on heart disease. There has been no satisfactory book available on congenital heart disease, and it is believed that this exposition will meet the requirements of all interested in such abnormalities. The author shows how to arrive at a correct diagnosis by means available to most physicians. From the history and development of the child, the presence or absence of cyanosis, the physical findings, and extremely important, the fluoroscopic study of the chambers of the heart and the size and pattern of the great vessels, with help from the electrocardiogram in certain conditions, she logically deduces the main pattern of the defect. Methods such as catheterization of the heart and x-ray studies following the injection of a radio-opaque dye are described, but are not stressed as being necessary to come to an understanding of the lesion at hand. The author points out that the clinical diagnosis of congenital lesions is often not possible in early infancy, but must await the development of the heart in the post natal period. The chapter on "The Physiology of the Malformed Heart and Diagnostic Principles" is excellent; and indeed much of the latter can be applied to the diagnosis of heart lesions in adults. Surgical treatment of coarctation of the aorta, persistent ductus arteriosus, and pulmonary stenosis are discussed.

The book is well illustrated by understandable diagrams of the circulation in the various lesions discussed, x-rays, and photographs and drawings of pathological specimens. It is highly recommended. The publishers have also done an excellent piece of work, and it is a pleasure to read such a well set up volume.

W. S. L.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Autoxidation of Diethyl Ether and Its Inhibition by Diphenylamine: A chemical, biological and clinical study of some practically important problems concerning the protection of anesthetic ether against disintegration. By GUNNAR LINDGREN. 190 pages; 23 × 14.5 cm., paper bound. 1946. Acta Chirurgica Scandinavica, c/o Norstedt & Soner, Stockholm 2. Price, 12:— Swedish crowns.

Blood Pressure and Its Disorders, Including Angina Pectoris. 2nd Ed. By JOHN PLESCH, M.D., Budapest, etc. 307 pages; 22.5 × 14.5 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, \$6.00.

Cardiopatías Congénitas de la Infancia. By DR. AGUSTIN CASTELLANOS Y GONZALEZ, Profesor Agregado de la Catedra de Patología y Clínica Infantil de la Universidad de la Habana, with the collaboration of DR. L. A. CABRERA. 406 pages (and atlas); 23.5 × 16 cm. 1948. Manuel V. Fresneda, Havana. Price, \$9.00.

Diabetes Mellitus in General Practice. By ARTHUR R. COLWELL, M.D., Associate Professor of Medicine and Director of Medical Specialty Training, Northwestern University Medical School, etc. 350 pages; 21 × 14.5 cm. 1947. Year Book Publishers, Inc., Chicago. Price, \$5.25.

Diseases of the Joints and Rheumatism. By KENNETH STONE, D.M. (Oxon.), M.R.C.P., Honorary Physician, B.R.C.S. Clinic for Rheumatism, London, etc. 362 pages; 23.5 × 16 cm. 1947. Grune & Stratton, Inc., New York. Price, \$6.50.

Endocrine Therapy in General Practice. 6th Ed. By ELMER L. SEVRINGHAUS, M.D., F.A.C.P., Formerly Professor of Medicine, University of Wisconsin, etc. 264 pages; 21 × 14.5 cm. 1948. Year Book Publishers, Inc., Chicago. Price, \$4.00.

Experimental Air-Borne Infection: Equipment and Methods for the Quantitative Study of Highly Infective Agents; Basic Data on Their Use Obtained with Phenol Red, Serratia Marcescens and Bacillus Globigii; and Preliminary Experiments on the Stability and Infectivity for Laboratory Animals of Air-Borne Clouds of Brucella Suis, Malleomyces Mallei, Malleomyces Pseudomallei, Pasteurella Tularensis, and of Viruses of the Psittacosis Group. By THEODOR ROSEBURY, with the co-authorship and assistance of the staff of the Laboratories of Camp Detrick, Maryland. 222 pages; 23.5 × 15.5 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, \$4.00.

Illustrative Electrocardiography. 3d Ed. By JULIUS BURSTEIN, A.B., M.D., Visiting Electrocardiographer and Chief of the Cardiac Clinic, Morrisania City Hospital, New York, etc., and NATHAN BLOOM, M.D., F.A.C.P., Associate Professor of Medicine and Chief of the Department of Electrocardiography, Medical College of Virginia, Richmond. 309 pages; 24.5 × 16 cm. 1948. D. Appleton-Century Company, New York. Price, \$6.00.

An Introduction to Gastro-enterology: A Clinical Study of the Structure and Functions of the Human Alimentary Tube. By JAMES DUNLOP LICKLEY, M.D., Hon. Consulting Physician, Sick Children's Hospital, Newcastle-upon-Tyne, etc. 143 pages; 19 × 12.5 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, \$3.00.

- Medicine: Volume I—The Patient and His Disease.* By A. E. CLARK-KENNEDY, M.D., F.R.C.P., Fellow of Corpus Christi College, Cambridge, etc. 383 pages; 24.5 × 15.5 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, \$6.00.
- Sexual Behavior in the Human Male.* By ALFRED C. KINSEY, Professor of Zoology, Indiana University; WARDELL B. POMEROY, Research Associate, Indiana University, and CLYDE E. MARTIN, Research Associate, Indiana University. 804 pages; 24 × 16 cm. 1948. W. B. Saunders Company, Philadelphia. Price, \$6.50.
- Tercer Congreso Interamericano de Cirugia: Tomo III.* Presidente: DR. DOMINGO PRAT. 662 pages; 24.5 × 17 cm. 1946 (October). Secretaria: Agraciada 1464 —Piso 13.
- Tercer Congreso Interamericano de Cirugia: Tomo II.* Presidente: DR. DOMINGO PRAT. 582 pages; 24.5 × 17 cm. 1946 (October). Secretaria: Agraciada 1464 —Piso 13.
- The Treatment of Rheumatism in General Practice.* 4th Ed. By W. S. C. COPEMAN, O.B.E., M.A., M.D. (Cantab.), F.R.C.P. (London), Physician in Charge, Department of Chronic Rheumatic Diseases, West London Hospital. 258 pages; 22.5 × 14.5 cm. 1946. The Williams & Wilkins Company, Baltimore. Price, \$4.00.
- Treatment of Some Chronic and 'Incurable' Diseases.* 2nd Ed. A. T. TODD, O.B.E., M.B. (Edin.), M.R.C.P. (Lond.), Honorary Physician, Bristol Royal Infirmary. 324 pages; 22.5 × 14.5 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, \$7.00.

COLLEGE NEWS NOTES

NOMINATIONS FOR A.C.P. ELECTIVE OFFICES, 1948-49

In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1948-49, are herewith announced and published:

President ElectReginald Fitz, Boston, Mass.
First Vice PresidentWilliam S. Middleton, Madison, Wis.
Second Vice PresidentMaurice C. Pincoffs, Baltimore, Md.
Third Vice PresidentCharles E. Watts, Seattle, Wash.

Regular elections will take place at the 1948 Annual Session in San Francisco, April 19-23. The Annual Business Meeting will be held Thursday afternoon, April 22, in Polk Hall of the Civic Auditorium.

The election of nominees shall be by the Fellows and Masters of the College. The above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations for members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-Laws.

Respectfully submitted,
Walter B. Martin, Norfolk, Va.
Edgar V. Allen, Rochester, Minn.
George H. Lathrope, Newark, N. J.
Edward L. Turner, Seattle, Wash.
William D. Stroud, Chairman, Philadelphia, Pa.
Committee on Nominations

ADDITIONAL LIFE MEMBERS

The American College of Physicians announces that the following Fellows became Life Members of the College by recent subscription:

Julius Bauer, Los Angeles, Calif.
David Beck, New York, N. Y.
Reuben Berman, Minneapolis, Minn.
Wyndham B. Blanton, Richmond, Va.
Meyer Bloom, Johnstown, Pa.
T. Homer Coffen, Portland, Ore.
Charles Cramer, Jackson Heights, N. Y.
Joseph S. D'Antoni, New Orleans, La.
Harold Freed, Dallas, Tex.
John L. Gompertz, Oakland, Calif.
Alfred S. Hartwell, Honolulu, T. H.
James H. Herndon, Dallas, Tex.
Byron J. Hoffman, Atlanta, Ga.
L. Winfield Kohn, New York, N. Y.
Abbe A. Ledbetter, Houston, Tex.
Harry R. Lipton, Atlanta, Ga.
William L. Lowrie, Jr., Detroit, Mich.
Warren S. Lyman, Ottawa, Ont., Can.
Willard Machle, New York, N. Y.
Jerome A. Marks, New York, N. Y.

Ralph McReynolds, Quincy, Ill.
Leo J. Meienberg, Portland, Ore.
Murlin P. Merryman, Rapid City, S. D.
Carlisle Morse, Louisville, Ky.
Max K. Newman, Detroit, Mich.
Lawrence Parsons, Reno, Nev.
Abraham Penner, New York, N. Y.
Lawrence E. Putnam, Washington, D. C.
Marjorie E. Reed, Plymouth, Pa.
Harold E. Richardson, St. Paul, Minn.
Andrew S. Robinson, Akron, Ohio
Percy K. Smith, Wichita Falls, Tex.
Robert L. Smith, Jr., San Francisco, Calif.
William H. Stoner, Bloomfield, N. J.
Robert T. Sutherland, Oakland, Calif.
Walter C. Swann, Huntington, W. Va.
Herman Tarnower, Scarsdale, N. Y.
Frederick R. Taylor, High Point, N. C.
A. M. Wehenkel, Detroit, Mich.
Sumner M. Wells, Jr., Grand Rapids, Mich.
Charles P. Wilson, Portland, Ore.
McIver Woody, New York, N. Y.
Paul H. Wosika, Chicago, Ill.

FELLOWSHIP IN ALLERGY AVAILABLE AT NORTHWESTERN UNIVERSITY

The Division of Allergy, Northwestern University Medical School, announces a fellowship for training in allergy. Candidates should have experience in research or in basic sciences. The Fellow will receive training in clinical allergy and in research and may register for an M.S. degree. This training is approved by the various Boards and by the Council on Medical Education and Hospitals of the A. M. A. Stipend is from \$1800 to \$3000. A similar training, without stipend, is also offered to a candidate whose qualifications do not meet fellowship requirements. For information address Dr. Samuel M. Feinberg, Northwestern University Medical School, Chicago, Ill.

INTERNATIONAL CONGRESS ON MENTAL HEALTH

The International Committee for Mental Hygiene is sponsoring a congress in London, England, August 11-21, 1948, which will feature three conferences, the first concerning child psychiatry, having as its theme personality development with special reference to aggression. The second conference will deal with medical psychotherapy with reference to guilt. These two conferences will occur August 11 to 14. The third conference, August 16-21, will concern mental hygiene and have as its theme mental health and world citizenship. A primary purpose of the Congress is to facilitate the exchange of scientific knowledge and experience which was acquired during the war, in social studies. There will be from 1000 to 2000 participants from many countries of the world; more than 500 are expected to come from the United States. For an effective congress involving so many scientists it has been found necessary to arrange for discussion groups to outline the program in advance. There are 83 such groups presently at work in the United States and 50 in other countries.

An International Preparatory Commission is planned which will meet before the Congress to receive reports from the discussion groups and to prepare recommenda-

tions which may be adopted by the Congress for submission to the World Health Organization and UNESCO.

Membership is open to trained workers in mental health and related subjects. The Executive Officer is Nina Ridenour, Ph.D., International Committee for Mental Hygiene, Inc., 1790 Broadway, New York 19, N. Y. Jonathan C. Meakins, M.D., F.A.C.P., Montreal, is Vice President of the organization and Henry W. Brosin, M.D., F.A.C.P., Chicago, C. Charles Burlingame, M.D., F.A.C.P., Hartford, Conn., and William C. Menninger, M.D., F.A.C.P., Topeka, Kans., are members of the Governing Board.

The Mississippi Valley Medical Society, of which Willard O. Thompson, M.D., F.A.C.P., Chicago, Ill., is President, will hold its 1948 annual meeting, September 29 to October 1 at Springfield, Ill.

The Joint Committee for the Coördination of Medical Activities, of which Ernest E. Irons, M.D., F.A.C.P., is Chairman, met in Chicago, December 6, 1947. The Committee discussed the following subjects: Navy training for medical aides in the Pacific Islands, school health and physical education program, problems affecting the general practitioner, pending legislation affecting medical practice, the Hospital Survey and Construction Program, nursing problem, rural medical service, World Medical Association, graduate education for medical officers, surplus war medical supplies, and outbreaks among the new-born in hospitals. The minutes of meetings of the Joint Committee are published in full periodically in The Journal of the American Medical Association.

American Overseas Aid is a federation of major voluntary foreign relief agencies which has been designated by President Truman to handle American participation in the world-wide United Nations Appeal for Children. Thus the one campaign for \$60,000,000 beginning in February, will provide funds for 24 private overseas relief agencies and the International Children's Emergency Fund, the United Nations agency which will administer funds collected by the United Nations Appeal for Children.

RECENT REGIONAL MEETINGS

Southern California, Los Angeles, January 23, 1948. A formal dinner meeting was arranged by the local Governor, Leland P. Hawkins, M.D., F.A.C.P., at the California Club. Lee A. DuBridge, President of the California Institute of Technology, was the guest speaker; his subject was "Science and the Future."

Virginia, Charlottesville, February 12, 1948. This meeting was held under the chairmanship of Staige D. Blackford, M.D., F.A.C.P., President of the Virginia section of the College. The following papers were presented in the afternoon session at the University of Virginia: "Recent Advances in Etiology and Therapy of Portal Cirrhosis," by H. B. Mulholland, M.D., F.A.C.P., and Thomas S. Edwards, M.D.; * "Effect of Fever on Liver Function," by Byrd S. Leavell, M.D., F.A.C.P., and Myer Hicks, M.D.; * "Electrophoretic Studies in Heart Disease," by Preston B. Lowrance, M.D.,* and Alfred Chanutin, M.D.; * "Relative Rates of Renal Excretion of Sodium and Chloride Ions in Normal, Heart Failure and Hypertensive Subjects," by Andrew J. Crutchfield, M.D.,* and J. Edwin Wood, Jr., M.D., F.A.C.P., College Governor for Virginia; "Use of Curare in Muscular Spastic States," by Walter Klingman, M.D., F.A.C.P.; "Psychosomatic Treatment," by Andrew D. Hart, Jr., M.D., F.A.C.P.;

* By invitation.

"Lipid Studies in Disease," by H. Rowland Pearsall, M.D.,* and Alfred Chanutin, M.D.;* "Effects of Nitrogen Mustards on Hematopoietic Organs," by J. E. Kindred, M.D.;* "Treatment of Leukemia with Urethane," by Howard P. Holt, M.D.,* and Byrd S. Leavell, M.D., F.A.C.P.; "Chemical Composition of Thymoma," by Thomas N. Warren, M.D.,* and Alfred Chanutin, M.D.* A reception and informal dinner at the Farmington Country Club followed the scientific session.

Texas, Arkansas, Louisiana, Mississippi and Tennessee, Houston, Tex., February 27 and 28, 1948. This was the first Regional Meeting to be held in Texas. The College Governors for the participating states presided over the sessions. Dr. Hugh J. Morgan, President of the College, addressed the dinner meeting on February 27 on the subject, "The Rôle of the American College of Physicians in American Medicine," and conducted a clinical-pathological conference the next day. Papers were presented by the following physicians: Julius H. Comroe, Jr., F.A.C.P., Philadelphia, Pa., "New Autonomic Drugs"; Oliver C. Melson, F.A.C.P., Little Rock, "Differential Diagnosis of Upper Abdominal Lesions"; Charles T. Stone, F.A.C.P., Galveston, "Infectious Hepatitis"; Edwin L. Rippy, F.A.C.P., Dallas, "Perpetuation of Psychosomatic Disorders by the Physician"; John K. Thompson, Associate, Fort Smith, "Congenital Toxoplasmosis"; Daniel E. Jenkins, Associate, Houston, "Streptomycin in the Treatment of Certain Forms of Tuberculosis"; Douglas H. Sprunt, F.A.C.P., Memphis, "The Effect of Nutrition on Viral Diseases"; Lucian M. Ferris, Associate, and T. H. Martin,* Vicksburg, "Use of Sympathetic Nerve Blocks in the Ambulatory Patient"; Samuel A. Shelburne, F.A.C.P., Dallas, "Long-term Study of Retinal Vessels in Hypertensive Patients"; A. Gayden Ward, F.A.C.P., Jackson, "Patent Ductus Arteriosus—A Report of Three Cases Successfully Treated by Surgery"; Don W. Chapman, Associate, Houston, "Venous Catheterization of the Heart in the Diagnosis of Congenital Heart Diseases"; G. M. Anderson,* New Orleans, "Prevention of Thrombo-Embotic Complications in Congestive Heart Failure"; Raymond L. Gregory, F.A.C.P., Galveston, "Unusual Diseases Affecting the Kidney"; William L. Marr, F.A.C.P., Galveston, "Refractory Anemias"; R. A. Hettig,* Houston, "Nitrogen Mustard Therapy in Blood and Lymph Dyscrasias." Chairmen of the Program and Arrangements Committees were James A. Greene, F.A.C.P., and DeWitt H. Hotchkiss, Jr., Associate, respectively, of Houston.

* By invitation.

OBITUARIES

DR. CLARENCE ORION CHENEY

Clarence Orion Cheney, M.D., F.A.C.P., died November 4, 1947, at White Plains, N. Y., at the age of 60. A well-known psychiatrist and former president of The American Psychiatric Association, he had been a Fellow of The American College of Physicians since 1939.

Dr. Cheney was born in Poughkeepsie, N. Y., July 10, 1887. He received the A.B. degree from Columbia University in 1908, and the M.D. degree from the College of Physicians and Surgeons, Columbia University, in 1911. Following an internship at Manhattan State Hospital, he was appointed Assistant Physician and Pathologist at that hospital from 1912 to 1917. From 1917 to 1922 he served as Assistant Director of the New York State Psychiatric Institute and Hospital in New York City. In 1922 he became Assistant Superintendent of the Utica State Hospital and in 1926 was appointed Superintendent of the Hudson River State Hospital at Poughkeepsie, N. Y. He left this post in 1931 to accept The Directorship of the New York State Psychiatric Institute and Hospital. Leaving the New York State service after twenty-five years, he became Medical Director of the New York Hospital, Westchester Division, in White Plains, N. Y., in 1936, which position he resigned in 1946. Throughout this period of thirty-five years of association with psychiatric hospitals he maintained a vigorous interest in studies of their problems, in teaching and in research. At Manhattan State Hospital he had done research in epilepsy, cerebral arteriosclerosis, on the spirochetes pallidae in the brains of paretics and on nerve cell changes in dementia praecox. At the New York State Psychiatric Institute he did special research in the relation of focal infection to mental disorders, and in his posts as administrator and director was a stimulating influence upon his staff in carrying out numerous research projects.

He was a successful and interested teacher, accepting appointment as Instructor in Psychiatry at Cornell University Medical College in 1914 where he was also Attending Physician and Chief of Clinic at The Cornell Dispensary. From 1917 to 1918 he was Instructor in Psychiatry at New York University and Bellevue Medical School, giving the entire course in Psychiatry both at Cornell Medical College and this school during that war year. In 1922, while at the Utica State Hospital he served as Instructor in Psychiatry at Syracuse University Medical School and was Attending Physician at the Utica Free Dispensary. When he went to Poughkeepsie in 1931, he became Professor of Clinical Psychiatry at the College of Physicians and Surgeons, Columbia University, and in 1932 Professor of Clinical Psychiatry and Executive Officer of the department at the same college. From 1935 to 1936 he was Representative of the Medical Faculty on the University Council at Columbia University. Upon his resignation from state appointments and acceptance of the Directorship at the New York Hospital Westchester Division, he became Professor of Clinical Psychiatry at Cornell University Medical College which position he held until his death.

He was an organizer and charter member of The American Board of Psychiatry and Neurology and was certified by this Board in 1934. He was certified as a Qualified Psychiatrist by the Board of Psychiatric Examiners of The New York State Department of Mental Hygiene in 1937, and was Representative of The New York State Medical Society on this Board of Examiners since 1944. He also served on various special commissions on hospital, sociological and post-war planning problems. Active as a member of the local Draft Board in New York City in World War I, he was Psychiatrist to the Medical Advisory Board of Westchester County during World War II, and at the time of his death was Consultant in Psychiatry to the Veterans Administration in New York City.

He participated actively in local and national medical societies, serving as Secretary and Treasurer of The American Psychiatric Association from 1928 to 1933, and as President in 1935-36. From 1933 to 1935 he was President of the New York Society for Clinical Psychiatry and served as Secretary and Chairman of the Section on Neurology and Psychiatry of The New York State Medical Society. In 1927-28 he was elected President of the Dutchess County Medical Society and was Chairman of the Committee on Mental Health from 1937 to 1942 of the Westchester County Medical Society. He was also an honorary member of The Southern Psychiatric Association, and corresponding member of the Royal Medico-Psychological Association of England.

He was Consulting Psychiatrist to seven hospitals, was a member of the White Plains Rotary Club, University Club, Sigma Xi and Alpha Omega Alpha.

In addition to this active participation in psychiatric progress, he found time to act as Associate Editor of The American Journal of Psychiatry from 1931, and as Associate Editor of The Psychiatric Quarterly from 1933.

The loss of Dr. Cheney will be deeply felt by the psychiatric profession and particularly by his many friends and former students.

CURTIS T. PROUT, M.D., F.A.C.P.

DR. WILLIAM PEPPER

Dr. William Pepper, Dean Emeritus of the University of Pennsylvania School of Medicine, died December 3, 1947, at the age of 73.

Dr. Pepper retired two years ago after serving as Dean of the Medical School for 33 years. His death was attributed to coronary thrombosis. He was the third William Pepper to serve the University of Pennsylvania in a distinguished position. His grandfather held the chair of theory and practice of medicine from 1860 to 1864, and his father was provost and professor of medicine from 1881 to 1894. Dr. Pepper was a cousin of the former U. S. Senator George Wharton Pepper and a direct descendant of Benjamin Franklin. He held the degrees of A.B., M.D., and D.Sc., from the University of Pennsylvania and an honorary doctorate of laws from Temple University. He contributed many articles to leading medical journals and was a member of many scientific societies and a former President of the Association of American Medical Colleges. He was also a trustee of the University of Pennsylvania. He is survived by two sons, William Pepper, Jr., an officer of the Philadelphia Free Library, D. Sergeant Pepper, M.D., F.A.C.P., Assistant Medical Director of the Provident Mutual Life Insurance Company, a daughter, Mrs. Mary Pepper Parker, and a brother, O. H. Perry Pepper, M.D., M.A.C.P., Professor of Medicine in the University of Pennsylvania.

All of the many who knew Dean Pepper will recall the sympathetic and good humored interest with which those who consulted him were received, and the absolute integrity which even the most casual acquaintance perceived in him. His long and distinguished career covered a vital period of transition in medical education. In his passing American medicine has lost one of its links with the past.

DR. RICHARD RAY DALRYMPLE

Dr. Richard Ray Dalrymple, F.A.C.P., died in the Warren General Hospital, Warren, Pa., on October 19, 1947. Dr. Dalrymple was born at Warren, Pa., on June 4, 1891, attended the local public schools, Bellefonte Academy, and received his medical degree from Jefferson Medical College of Philadelphia in 1920. He was in the practice of internal medicine at Erie, Pa., for several years and then removed to Fond du Lac, Wis., and thereafter, at the opening of World War II, he entered the Medical Corps of the U. S. Army, advancing to the rank of Lieutenant Colonel. His death was due to tuberculosis. He had been a Fellow of the American College of Physicians since 1929.

DR. GEORGE HERBERT EVANS

Dr. George Herbert Evans was born in Ontario, Can. He came to the United States in his early years. After finishing public schools he took his medical degree at Detroit College of Medicine and Surgery in 1891. He went immediately to San Francisco and began the practice of his profession, which he continued until his retirement in 1933.

He possessed elements of leadership which he showed in many ways. He early became interested in tuberculosis, and gave it much of his time, although he considered internal medicine his field of practice.

In 1903, the Medical Society of the State of California appointed a committee to study the question of tuberculosis in the state. Dr. Evans was a member of that committee. It worked in harmony with the Southern California Antituberculosis League which had been established the year before, the chief aim of which was educational and organizational.

It was under the auspices of the state committee, in 1904, that Dr. Evans called the meeting at which the San Francisco Tuberculosis Association was formed. He was active in local, state, national and international tuberculosis associations. He was active in forming the California Tuberculosis Association and served as its president in 1912. He was a delegate to the Fifth International Tuberculosis Congress in Paris in 1905, and the Sixth, in Washington in 1908.

He was active in the formation of and was Director of the "Tuberculosis Colony," instituted by the San Francisco Department of Health in 1906, the first attempt of the city to isolate those suffering from active tuberculosis.

He was an active member of many medical societies, and served as Secretary of the Medical Society of the State of California in 1903. He was a past President of the San Francisco County Medical Society, the Medical Society of the State of California, the California Academy of Medicine, the American Therapeutic Society, and the California Tuberculosis Association; and a Fellow of the American Medical Association and the American College of Physicians.

In 1903 he was a member of the "Health Committee" which was instrumental in securing an unwilling coöperation on the part of the state and municipal authorities to recognize the presence of plague in the city and to initiate steps for its eradication and future prevention.

In 1913 he was appointed Assistant Clinical Professor of Medicine in the University of California, and organized the Department of Tuberculosis. He was an active teacher until 1933.

After his retirement he spent much time abroad, particularly in England and Italy, studying tuberculosis, housing, archeology, and medical history. He published an unusually interesting description of a visit to Harvey's tomb. He had compiled many notes which were to serve as the basis for future contributions. His study of the early history of tuberculosis in California shows that the first mention of tuberculosis among the settlers was among the Russians who came down from Alaska and settled along the northern California coast.

Dr. Evans had wide interests, was a good conversationalist, and a charming companion. He was a member of the Bohemian Club and the Commonwealth Club of San Francisco, and the Author's Club of London.

In April, 1947, he received one of the first medals awarded by the California Tuberculosis and Health Association for outstanding service in the cause of tuberculosis.

Dr. Evans died of a cerebral hemorrhage September 5, 1947, in his seventy-eighth year, after a full life of accomplishment.

F. M. POTTENGER, M.D., F.A.C.P.,
Monrovia, Calif.

COLONEL JOHN T. AYDELOTTE

Colonel John T. Aydelotte, a Fellow of the American College of Physicians since 1930, died July 5, 1947, in Brooke General Hospital, Fort Sam Houston, Tex., where he had been taken from his home in San Antonio.

Born August 28, 1884, in Ocean City, Md., he was graduated from Jefferson Medical College of Philadelphia in 1906. He joined the Medical Reserve Corps of the Army on September 1, 1909, and after graduating from the Army Medical School, Washington, D. C., in 1910, was commissioned a First Lieutenant in the Medical Corps, Regular Army, May 8, 1910. The next fifteen months were spent at Fort Sam Houston, and then he was sent to the Philippine Islands for a normal tour of duty. He spent the next four years in various camps and posts in California, Wyoming, Texas and Arizona. In June, 1918, he became Camp Surgeon at Camp MacArthur, Tex.

After a period of instruction at Army War College, Washington, D. C., and a year's service in camps in Alabama, Mississippi, and Kentucky, he was sent to General Hospital No. 11, Camp May, N. J., for special instruction in the diagnosis and treatment of peripheral nerve injury cases. Then he became Chief of the Neuropsychiatry Section at General Hospital No. 6, Fort McPherson, Ga.

When the R.O.T.C. Unit was established at Jefferson Medical College of Philadelphia, Colonel Aydelotte was chosen as a Professor of Military Science and Tactics there, and the success of that unit was due largely to his tact, personality, and good judgment, which won friends for himself and the unit from the very beginning.

He also served as Surgeon at Fort Slocum, N. Y., and, after four years at Fitzsimons General Hospital, Denver, Colo., was sent to China. He was retired from the service at Fort Devens, Mass., May 31, 1936.

DR. EDWARD JOHN KEPLER

Edward John Kepler, M.D., F.A.C.P., of Rochester, Minn., died October 19, 1947. He had known for many months that he was seriously ill with coronary arteriosclerosis.

Dr. Kepler, a graduate of the University of Minnesota Medical School, was born at Erie, Pa., January 22, 1894. He received the B.S. degree from Pennsylvania State College in 1916, and the M.B., M.D. and M.S. degrees from the University of Minnesota subsequently. Following an internship in the Philadelphia General Hospital, Dr. Kepler was appointed Fellow in Medicine in the Mayo Foundation in 1925. He rose to become Professor of Medicine in the University of Minnesota (Mayo Foundation), and Associate in Medicine in the Mayo Clinic. He was a diplomate of the American Board of Internal Medicine.

Dr. Kepler became a Fellow of the American College of Physicians in 1938. He was also a Fellow of the American Medical Association, and a member of the Olmsted-Houston-Fillmore-Dodge Counties Medical Society, the Central Society for Clinical Research and the Association for the Study of Internal Secretions.

Dr. Kepler was a physician with intense curiosity about the unknown in medicine; almost every patient raised problems in his mind which were outside ordinary medical thinking. His philosophic approach to medical problems and to life in general endeared him to his colleagues and students. His death removed from medical circles one of those rare individuals with really great minds and, from his circle of friends, a beloved individual.

E. V. ALLEN, M.D., F.A.C.P.,
Governor for Minnesota

DR. H. MILTON CONNER

H. Milton Conner, M.D., F.A.C.P., of Rochester, Minn., died October 18, 1947, at the age of 66 years; for several years prior to his death he had been confined to bed, a victim of severe Parkinson's disease. He is remembered by his associates in the Mayo Clinic and the Mayo Foundation as a valued friend and as a splendid clinician who had the welfare of his patients foremost in his mind.

A graduate of the Kansas Medical College, Topeka, Dr. Conner served that school from 1910 to 1913 as Professor of Pathology. He later joined the staff of the Mayo Clinic as Consulting Physician, and held appointment in the University of Minnesota (Mayo Foundation) as Associate Professor of Medicine. He was a diplomate of the American Board of Internal Medicine.

Dr. Conner was a member of the Olmsted-Houston-Fillmore-Dodge Counties Medical Society, of the Minnesota State and Southern Minnesota Medical Associations, Minnesota Society of Internal Medicine, Central Society for Clinical Research, and the Societe Francaise d'Hematologie. He was a Fellow of the American Medical Association, and, since 1922, of the American College of Physicians.

E. V. ALLEN, M.D., F.A.C.P.,
Governor for Minnesota

DR. JAMES ANDREW FOUNTAIN

James Andrew Fountain, M.D., F.A.C.P., of Macon, Ga., died June 26, 1947, following a heart attack. He was 54 years of age.

Dr. Fountain, who graduated from Vanderbilt University School of Medicine in 1917, was a veteran of World War I, when he served as a medical officer in the Navy. He practiced medicine in Macon for 26 years. He was a member of the Bibb County Medical and Georgia State medical societies. He had been a Fellow of the American College of Physicians since 1931.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,
Governor for Georgia

DR. MARGARET ANN GOULD

Dr. Margaret Ann Gould, an Associate member of the College since 1925, and a competent and sympathetic practitioner, died October 30, 1947. Quiet and modest, and always faithful to her responsibilities, Miss Gould had a host of friends, as well as loyal patients who counted on her for tactful guidance and professional care.

Born in 1870, Dr. Gould received her medical training at Trinity Medical College, Toronto, in 1898. She interned at the Women's Hospital in Philadelphia, and took up general practice in Pittsburgh in 1903.

After a career of great usefulness she retired in May, 1941, and spent her winters thereafter in Florida. Dr. Gould was one of the first of the women physicians to practice in Pittsburgh. Her attractive personality, combined with kindness, tact, and unselfish devotion to her duties, won her the cordial coöperation and respect of her colleagues.

R. R. SNOWDEN, M.D., F.A.C.P.,
Governor for Western Pennsylvania

DR. FREDERICK JOHN POHLE

In the premature death of Frederick John Pohle on November 26, 1947, the American College of Physicians lost one of its most promising young members, and the University of Wisconsin Medical School a most valued investigator and teacher.

Dr. Pohle was born on May 1, 1906, at Bloomington, Wis., where he received his early education in the public schools. Later, after attending the La Crosse Normal

School, he taught in the Waukesha High School for one year before entering the University of Michigan where he received the degree of Doctor of Medicine in 1934. He then came to the State of Wisconsin General Hospital as an intern and assistant resident in medicine. From 1936 to 1938 he was a research fellow at Harvard Medical School and an assistant resident in medicine at the Thorndike Memorial Laboratory, Boston City Hospital. He returned to the University of Wisconsin Medical School in 1938 as a research associate; from 1940 to 1946 he was assistant professor of medicine, and physician to the State of Wisconsin General Hospital.

In January, 1941, he was activated as a Major with the 135th Medical Regiment, Wisconsin National Guard. He was later transferred to Station Hospital, Fort Bragg, N. C., where he served as Chief of Laboratory Service, with rank of Lieutenant Colonel, until his retirement from the Medical Corps of the Army of the United States in 1945.

Following his return to the University of Wisconsin Medical School, he was advanced to the rank of associate professor of medicine in 1946. He held this appointment at the time of his death, which followed an operation for subarachnoid hemorrhage.

Dr. Pohle's interest in medical research began when, as a medical student, he assisted in hematological research at the Simpson Memorial Institute. He published many authoritative papers subsequently, gaining for himself a national and international reputation, especially in the field of hematology. Recognition came to him through membership in many nationally important scientific societies, including Alpha Omega Alpha, Sigma Xi, The American Society for Clinical Investigation, The Central Society for Clinical Research, the Central Clinical Research Club. He was a diplomate of the American Board of Internal Medicine, and was elected an Associate of the American College of Physicians in October, 1946. He was also a member of the Dane County and Wisconsin Medical Societies, and a fellow of the American Medical Association.

Dr. Pohle is survived by his widow and their two daughters. The College extends its sympathy to them, and shares in their loss of husband, father, investigator, author, teacher and clinician.

KARVER L. PUESTOW, M.D., F.A.C.P.,
Governor for Wisconsin

DR. HAROLD IRWIN REYNOLDS

Harold Irwin Reynolds, M.D., F.A.C.P., of Athens, Ga., died on October 30, 1947, of chronic lymphatic leukemia.

Born at Lexington, Ga., in 1887, Dr. Reynolds obtained his medical degree in 1912 from the Johns Hopkins University School of Medicine; he had previously attended the University of Georgia and had received from it the degree of Bachelor of Arts. He subsequently served his alma mater as University Physician, in charge of the Crawford W. Long Infirmary. He was also a member of the medical staffs of the Athens General and St. Mary's Hospitals, and was regarded as an outstanding physician in the section of Georgia in which he practiced internal medicine.

Dr. Reynolds was a member of the Clarke-Madison-Oconee Counties and Eighth District Medical Societies, the Medical Association of Georgia and the Southern and American Medical Associations. He was elected to Fellowship in the American College of Physicians in 1927.

DR. COLIN GEORGE SUTHERLAND

On November 12, 1947, in his fifty-fifth year, death came suddenly to Dr. Colin G. Sutherland, Assistant Professor of Medicine in the McGill University Faculty of Medicine, and Physician to the Royal Victoria Hospital, in Montreal.

Born in Nova Scotia, and educated at Dalhousie University (B.A., 1913), he qualified as M.D., C.M. at McGill in 1917, serving in the Canadian Army Medical Corps in World War I prior to and after graduation. This was followed by a two year internship at the Royal Victoria Hospital, with Dr. Charles F. Martin in Medicine and, in Surgery and Urology, with Dr. A. E. Garrow and Dr. David MacKenzie, respectively. He then proceeded to the Johns Hopkins Hospital in Baltimore for a year with Dr. Tom Brown in Gastro-enterology, and subsequently returned to Montreal to enter practice with major interest in this specialty, and to join the hospital and teaching staffs of the Royal Victoria Hospital and McGill University.

During the late war, Dr. Sutherland served as Medical Consultant to the Department of Veterans Affairs and also had supervision of medical cases in the soldiers' ward, a responsibility which he discharged with characteristic efficiency and unremitting care.

He was a member of the Montreal Medico-Chirurgical Society, the Canadian Medical Association, and a Fellow of the American Gastro-Enterological Association. He was elected a Fellow of the American College of Physicians in 1931.

Forthright, vigorous, vital, sometimes refreshingly outspoken, he was intolerant of all insincerity and dissembling. He was implicitly trusted by his colleagues and patients, and warmly loved by his friends. Characteristic also was an infectious optimism which endeared him to many of his patients, enduing them as it did with patience and courage to hope and to endure. An ardent golfer, and an enthusiastic curler (fortunately they did not conflict) nevertheless his chosen profession and its heavy demands upon his time and energy were always paramount.

ARTHUR T. HENDERSON, M.D., F.A.C.P.,
Governor for Quebec

DR. BENJAMIN JAFFEE BIRK

Benjamin Jaffee Birk, M.D., F.A.C.P., was born in Michigan City, Ind., on August 17, 1894. He received his B.S. degree from the University of Indiana in 1916 and his M.D. degree from Rush Medical College in 1919. He then served internships in the Michael Reese and Cook County Hospitals, Chicago. He did postgraduate work at the University of Chicago School of Medicine, and furthered his studies in internal medicine at the University of Vienna in 1927-28.

As a Milwaukee physician for almost thirty years, Dr. Birk served as Chief Resident, Chief of Staff, Head of Division of Medicine, and finally Head of the Department of Internal Medicine of Mt. Sinai Hospital. From 1940 to 1942 he was an Instructor of Internal Medicine in the Marquette University School of Medicine.

During World War I Dr. Birk served in the Army Medical Corps. He was commissioned in the Army of the United States again in 1942 as a lieutenant-colonel. Before going overseas he was chief of medicine at Fort Sheridan, Ill., after which he was attached to the Chinese Combat Command of the United States Army for thirteen months. In 1944, he was awarded the Legion of Merit with oak leaf cluster for especially meritorious conduct. He was discharged in 1946 with rank of colonel.

Dr. Birk was a member of the Military Order of World Wars, Association of Military Surgeons of the United States, Wisconsin Military Association, Reserve Officers Association, American Medical Association, Wisconsin Heart Association, American Heart Association, Milwaukee Academy of Medicine, Milwaukee County and Wisconsin Medical Societies. He had been a Fellow of the American College of Physicians since 1939.

KARVER L. PUESTOW, M.D., F.A.C.P.,
Governor for Wisconsin

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THE EFFECTS OF SHOCK ON THE KIDNEY *

By DONALD D. VAN SLYKE, *New York, N. Y.*

THE type of "shock" here discussed is the condition, caused by hemorrhage, burns, trauma, dehydration, or other injury, in which there is an inadequate volume of blood to fill the vascular bed. The visible effects in man, prostration, cold perspiration, bloodless or cyanotic skin, etc., are familiar. It appears that similar renal effects can result from a period of peripheral circulatory failure due, not to decreased blood volume, but to cardiac failure, or to pooling of blood in part of the vascular bed; but the present discussion is limited to conditions of shock in which decreased volume of the circulating blood, resulting from loss of blood or plasma or from dehydration, is the primary cause.

The immediate and later effects of shock on the kidney, indicated by available data, will first be outlined. Experiments illustrating these effects will then be presented.

The First, or Ischemic, Phase of Shock Kidney. The immediate effects of shock on the kidney are circulatory. Renal blood flow is diminished, and with it renal excretory function.^{1, 2, 3} The decrease may be so great that complete anuria results. However, if the renal ischemia is not too complete and prolonged, the kidney cells are not injured, and restoration of normal general circulation is followed by recovery of normal renal function within a short time. A lag period of an hour or more may intervene, due perhaps to continued constriction of renal vessels, after the general circulation is restored before renal function recovers, but then normal excretion is resumed.

The initial shutdown of the renal circulation appears to be part of a defense reaction of the organism to loss of circulating blood volume; the vascular bed is contracted by peripheral constriction so that the diminished volume of available blood will be adequate to supply the vital organs, such as the brain, whose function must be maintained to avoid immediate death. If

* From an address given at the Twenty-Eighth Annual Session of the American College of Physicians, Chicago, April 30, 1947.

From The Hospital of The Rockefeller Institute for Medical Research, New York 19, New York.

blood loss is severe, the kidneys are included in the constricted periphery; the necessity for this inclusion is obvious from the fact that the kidneys in the resting subject normally receive about 20 per cent of the blood.

Fall in blood pressure below 40 to 60 mm. systolic is in itself sufficient to cause anuria because the pressure is insufficient to maintain glomerular filtration.* In shock, however, failure of renal function often occurs before blood pressure falls to such levels (see figure 5, this paper). It appears that renal failure during shock usually owes its onset to renal vasoconstriction,† and that, even in cases where the blood pressure falls below 60 mm., constriction of the renal vessels occurs before the falling blood pressure reaches this level.

With regard to the solicitude with which their blood supply is maintained in time of deficit, the kidneys appear to stand intermediate between the skin and skeletal muscles,⁵ which can survive long periods of ischemia, and the central nervous system, which can survive almost none. If the deficit of circulating blood volume is sufficiently severe and prolonged, the kidneys are sacrificed in the apparent attempt to maintain circulation through heart, lungs, and brain.

The Second, or Renal Damage, Phase of Shock Kidney. If shock is severe and prolonged, restoration of the general circulation and recovery from the circulatory symptoms of the shock may not be accompanied by resumption of normal renal excretion. Anuria or oliguria may persist, or urine of low specific gravity may be excreted; urea clearance is low. This period of complete or partial renal failure may last until fatal uremia develops in a period that may vary from two to 20 days.⁶ Or gradual return of function may occur, so that within the days of grace allowed, excretion

* Literature on the relation between arterial blood pressure and glomerular filtration is reviewed by Lassen and Husfeldt (Jr. Clin. Invest., 1934, xiii, 263) together with observations on subjects in whom blood pressure was lowered by spinal anesthesia.

† Trueta⁴ and his collaborators offer a different explanation for renal failure during acute shock. They have demonstrated, in a series of brilliant experiments with rabbits, that application of a tourniquet for a number of hours to the left hind leg of a rabbit caused a withdrawal of blood from the *left* renal cortex, while the total blood flow through the kidney was increased, as evidenced by the observations, that time required for blood to traverse the kidney was halved, that the blood issuing from the renal vein changed partially or wholly to arterial red color, and that the renal vein was swollen and showed pulsation of arterial type. These, and other data, indicated that the condition was caused by dilation of vascular channels through the medulla, causing the renal blood to rush through them, and to by-pass completely its channels through the cortex. It was suggested that this phenomenon, of apparently neurogenic origin, might, "by preventing blood from reaching the filter of the kidney in the cortex" cause the cessation of renal function "in hemorrhage or conditions with decreased blood volume." However, measurements by other investigators of renal blood flow during acute hemorrhagic and traumatic shock (for example see figure 5 of this paper) show that the total renal blood flow is not accelerated, as in the condition studied by Trueta, but is greatly diminished, and that in severe shock the renal blood flow approaches zero. Also the fact, illustrated in figure 1, that during acute hemorrhagic or traumatic shock, sufficiently severe to lower renal blood flow to a small fraction of normal, the kidneys continue to extract 85 to 90 per cent of para-amino hippurate from the plasma indicates that such blood as continued to perfuse the kidneys was supplying nephrons of normal excretory capacity. The phenomena observed by Trueta and his collaborators appear to be quite different from those that accompany shock from hemorrhage, dehydration, or trauma other than pressure on the legs.

becomes sufficiently restored to prevent uremia, and ultimate recovery of the kidneys may be complete.

Whereas, in its initial phase during acute shock, renal failure is a quickly reversible functional affair, renal failure persisting after recovery from shock is attributable to organic injury, and is reversible slowly and sometimes not at all. There is no sharp dividing line between the two phases: the purely functional failure due to lack of renal circulation passes during prolonged shock gradually into a condition of increasing organic damage.

Of anuria observed during acute shock the interpretation is different from that of anuria or depressed renal function persisting after recovery from shock. Anuria during shock indicates that the kidneys are subject to ischemia, which in a few hours in man may cause irreversible injury. After recovery from shock, persisting anuria or depressed function indicates that organic damage has occurred, but not necessarily that it is progressing. There is at least a partial resumption of renal blood flow, and repair of the damage may proceed, so that even several days of post-shock renal depression may be followed by recovery. In some cases, it is true, renal function partially recovered after shock may fail again, indicating progress of the lesion.

The Degree of Shock That Is Followed by Uremia. Uremia can develop from shock only when the latter is within a certain limited zone of severity and duration. The shock must be severe and prolonged in order to cause irreversible damage to the kidneys. But if it is too severe it causes death, usually from circulatory failure, before the patient has time to develop uremia. Presumably because the zone is narrow, renal failure is a cause of death in only a small percentage of the cases that survive shock. But the inability to stop the progress of uremia in such cases was a cause of major concern to surgeons in the late war. Thus, a letter from Dr. E. D. Churchill stated: "By excellent forward surgery and the liberal use of whole blood transfusion as well as plasma we are saving lives, but also keeping certain men alive temporarily only to display later kidney damage. There has been either complete anuria with death, or in one case a fall of urinary output to 200 c.c. with ultimate recovery of kidney function. This phenomenon is not unique to the 'crush syndrome,' but may occur in any wounded man who experiences a long period of greatly reduced volume flow."

Renal Lesions Caused by Shock. Lucké⁶ has examined kidneys from 538 army cases showing what he terms "lower nephron nephrosis." Although the original injuries were various, the histological kidney pictures were all similar: glomeruli and proximal tubules practically undamaged, distal convoluted tubules and thick tubules of Henle degenerated or showing actual necrosis. Of the 538 cases 403 were from subjects who had suffered the type of injury that produces shock, viz. battle wounds, crushing injuries, abdominal operations, burns, heat stroke (dehydration), while 67 were from cases of poisoning (sulfonamides, arsenicals, carbon tetrachloride, etc.).

Mallory⁷ has studied the lesions in some 260 cases of battle injury, and is able to draw conclusions concerning the time of appearance of the succes-

sive stages of the lesions: (1) Within 24 hours after injury, lipid vacuolization of the ascending limb of the loop of Henle; (2) twenty-four to 72 hours after injury precipitation of myoglobin or hemoglobin in the distal convoluted and collecting tubules; (3) sometimes on the third day, regularly on the fourth and fifth, necrosis and regeneration of epithelium in the ascending limbs and distal tubules. "Renal insufficiency was found to antedate all structural changes, but was never progressive in the absence of a definite pigment nephropathy." Mallory's observation, that visible lesions do not appear until a day or more after the original injury, indicates that the lesions are after-effects of damage, not histologically demonstrable, suffered by the tubular cells during shock. Mallory did not find the tubular lesions caused by temporary clamping of the renal artery in animals identical with those observed in human cases of post-shock renal damage, but Badenoch and Darmady⁸ found that the lesions produced in rabbits by such clamping resembled those observed in human cases.

The Cause of Organic Renal Damage. The renal ischemia that has been found to occur during severe shock^{1, 2, 3} appears to be the inciting cause of the changes that lead to the development of organic damage.^{1, 6} When approximately complete renal ischemia is produced in dogs by clamping the renal artery for two hours transitory partial renal failure results (figure 6), and such ischemia continued for three to four hours is followed by death in uremia¹ (figure 7). The duration of ischemia required to produce these effects is of the order of that required by severe shock to cause similar effects in man. The view that the primary cause of renal injury is probably ischemia suffered by the kidneys during shock has been adopted as the result of clinical observation by Darmady et al.⁹ and Maegraith.¹⁰

Corcoran and Page¹¹ and Mallory⁷ consider that deposits of hemoglobin products, forming in damaged tubules after the first to third day following injury,⁷ contribute to further progress of the tubular lesions that have been initiated by ischemia. That the tubular lesions typical of post-shock uremia can occur in man without the deposits, however, appears from the observation of Lucké,⁶ that in some of his cases the deposits were scanty or absent.

Mechanism of Renal Failure Persisting After Recovery from Shock. The similarity of the histological picture in the post-shock kidney to that caused by nephrotoxic poisons leads Lucké⁶ to consider that the mechanism of the anuria in both conditions is probably the same. The effects of nephrotoxic poisons had been observed by Richards¹² in the nephrons of frogs poisoned by mercuric chloride and other nephrotoxic substances. Filtration in the glomeruli of these frogs went on with normal rapidity, but *the entire filtrate was reabsorbed from the tubules*, so that no urine entered the bladder. In such a condition the cells of the tubular epithelium lose their normal power of selected reabsorption. By this power the normal kidney tubules return from the glomerular filtrate to the blood the solids whose retention is essential to the organism (glucose, amino acids, salts, etc.), together with the amount of water required to maintain normal hydration, while they bar the way to

return of waste products, such as urea, uric acid, creatinine, and superfluous water and electrolytes. In contrast to this selective reabsorption by the normal tubular wall, the tubular walls devitalized by poison in Richards' experiments appeared to approach dead membranes in their behavior, and to permit all the glomerular filtrate, both water and solids, to pass indiscriminately back into the blood of the tubular capillaries, presumably drawn by the osmotic attraction of the plasma proteins for the filtrate water, with anuria as the result.

Lucké's explanation of persistent post-shock renal failure is consistent with the observation (figure 1) that after experimental renal ischemia continued for two hours the tubules of dogs' kidneys lose most or all of their ability to extract para-amino hippurate from the renal blood plasma, indicating severe injury to tubular function. Another functional evidence of tubular injury is the commonly observed fact, that the kidney damaged by shock loses much or all of its ability to concentrate the glomerular filtrate. It appears that renal ischemia, such as occurs in man during shock, may be one of many nephrotoxic factors that produce "lower nephron nephrosis," with renal failure from tubular reabsorption.

Reabsorption must be considered as a tentative, rather than a demonstrated, explanation of post-shock renal failure, because total tubular reabsorption, such as was observed by Richards in the tubules of poisoned frogs, has not been demonstrated by such direct observation in the post-shock kidney. But the weight of evidence in favor of tubular reabsorption appears to be strong.

Some investigators have considered that post-shock uremia might be due to mechanical blockage of the tubular lumina by detritus staining like hemoglobin or a heme derivative. This explanation is rejected by Lucké⁶ because of frequent absence of upper tubular and capsular dilatation that would result from such obstruction, and because in many cases he found heme casts scanty or absent. Also the fact that in shock oliguria the urine gravity is low, despite the small volume, indicates that the renal injury is general, rather than localized to blocked nephrons. Mechanical obstruction as the cause of renal failure is also rejected by Bywaters,¹³ although both he and Corcoran and Page¹¹ and Mallory⁷ consider that the detritus forming in damaged tubules may contribute to the progress of the lesions initiated by ischemia.

Historical Résumé. Present concepts concerning the effects of shock on the kidney have developed from the studies of many investigators. The following résumé necessarily omits many of importance.

That the renal failure (first stage of shock kidney) accompanying hemorrhage, dehydration, and other conditions that have in common the peripheral circulatory signs of shock, could be due to decreased renal blood flow, was deduced by Fishberg¹⁴ from the fact that the urea clearance, which falls low in these conditions, had been experimentally observed¹⁵ to parallel physiological changes in renal blood flow. Fishberg suggested that the extraordinary

ischemia and vasoconstriction observed in the skin and limbs during shock might be shared by the kidneys.

The accuracy of Fishberg's deduction was confirmed when the Rockefeller Hospital group^{1, 3} measured the renal blood flow in hemorrhagic and traumatic shock (figure 5), and found it depressed in proportion to the severity of the shock. Lauson, Bradley, and Cournand² at the same time observed in human subjects in shock similar depression of the para-amino hippurate clearance, which has been found (figure 2) to parallel the renal blood flow in shock, provided the shock has not lasted long enough to cause organic renal damage.

That renal function can remain depressed after recovery from shock ("second stage" of shock kidney), so that death in uremia occurs some days later, was observed by Rogers¹⁰ over 30 years ago, in his classic studies of cholera, where shock is caused by dehydration. That similar uremia can occur after recovery from shock caused by trauma was noted by Bywaters¹³ in his description of the "crush syndrome" early in World War II. It is probably due to Bywaters' description of the crush syndrome that post-shock uremia was soon recognized as a not infrequent after-effect of severe battle injuries.

The facts, (1) that renal ischemia occurs during shock,^{1, 2, 3} (2) that renal ischemia caused by temporary occlusion of renal arteries in animals is followed by renal failure, either transitory or fatal depending on the duration of the ischemia,^{1, 17, 18, 19, 20} and (3) that similar periods of severe shock in man are followed by similar transitory or fatal renal failure, were presented by Van Slyke, Phillips, and their collaborators¹ as support for the hypothesis that renal failure persisting after shock is due to organic injury initiated during shock by ischemia.

Histological studies of Bywaters and his colleagues,¹³ Lucké,⁶ Mallory⁷ and others have revealed severe damage to the renal tubules, chiefly the distal tubule and loop of Henle, with little or no glomerular damage, as a constant finding in post-shock uremia. Observations by Mallory⁷ and by Corcoran and Page¹¹ indicate that debris of heme derivatives, forming in the tubules one or more days after onset of renal failure,⁷ may contribute to progress of tubular damage initiated by ischemia.

The identity of the tubular lesions with those caused by various nephrotoxic agents led Lucké to suggest that the cause of post-shock uremia may be, not failure of filtration in the glomeruli, but the same indiscriminate tubular reabsorption of glomerular filtrate and its excretory constituents that was noted by Richards¹² in the kidneys of frogs made anuric by nephrotoxic poisons. The probable validity of Lucké's explanation is supported by functional evidence of tubular damage, viz. the commonly observed inability of the kidneys in post-shock renal failure to excrete concentrated urine, and their decreased ability to extract para-amino hippurate from the renal blood.¹⁹

A series of renal circulatory phenomena, of quite different nature from those summarized above, but also leading to renal failure, has been recently

described by Trueta and his collaborators⁴ in animals following periods of pressure on the legs, and due apparently to pressure on the nerves. The renal blood flow is accelerated rather than retarded, but the blood courses through dilated medullary vessels and by-passes the renal cortex and its glomeruli. It appears that this phenomenon may account for some cases of renal failure in the "crush syndrome," but not for the renal effects of shock caused by hemorrhage, dehydration, circulatory failure, or trauma other than that of pressure on the limbs.

EXPERIMENTS ILLUSTRATING EFFECTS OF SHOCK AND RENAL ISCHEMIA ON THE KIDNEYS

Following are examples of experimental observations from our laboratory illustrating the immediate and later effects of shock and renal ischemia. The examples are taken from experiments carried out during the war by Drs. Phillips, Dole, Hamilton, Hiller, Emerson, and Archibald,^{1, 3, 19, 20} with support of the Committee of Medical Research of the Office of Scientific Research and Development, in the United States Naval Research Unit of the Hospital of The Rockefeller Institute.

The Immediate Effects of Hemorrhage and Traumatic Shock, and the After Effects of Renal Ischemia, on Tubular Function Measured by the Completeness with Which the Kidneys Extract Para-amino Hippurate from the Blood Plasma. While all evidence is to the effect that (in the kidneys of man and the dog) the normal excretory products, such as urea, creatinine, salts, etc., are removed from the renal blood by filtration of about 20 to 30 per cent of the plasma water and its crystalloid solutes in the glomeruli,²¹ certain foreign substances when injected into the blood stream evoke the additional aid of excretion by the tubules to obtain a more rapid clearance of these substances from the blood. Such substances are phenol red, diodrast, and para-amino hippurate. Of the para-amino hippurate³ entering the kidneys in the plasma of the renal artery, an average of about 87 per cent is removed by the kidneys of the normal dog^{*} and of man.²² Since only about 20 per cent is normally filtered in the glomeruli,²¹ it is evident that the greater part must be excreted by the tubules.

Figure 1 shows that in acute hemorrhagic or traumatic shock the kidneys continued to extract the PAH with this same degree of completeness, until the shock was so severe that the renal blood flow was decreased below 5 per cent of normal, an effect that was reached in these experiments only after shock was maintained during several hours by repeated hemorrhage or trauma. Until this extreme stage was reached the tubular cells retained their vitality and continued to excrete 85 to 90 per cent of the PAH from the plasma that perfused the kidney.

When, without hemorrhage or shock, the kidneys were submitted to two hours of ischemia^{1, 20} by clamping of the renal arteries, subsequent restoration of the renal blood flow was followed by a period during which only

* Para-amino hippurate will be designated by the symbol PAH.

10 to 20 per cent of the hippurate was extracted from the plasma (see solid circles, figure 1). If the clamp was left on for as long as four hours, anuria followed, with death in uremia four to eight days later,^{1, 20} as in human cases that fail to recover renal function after prolonged shock.

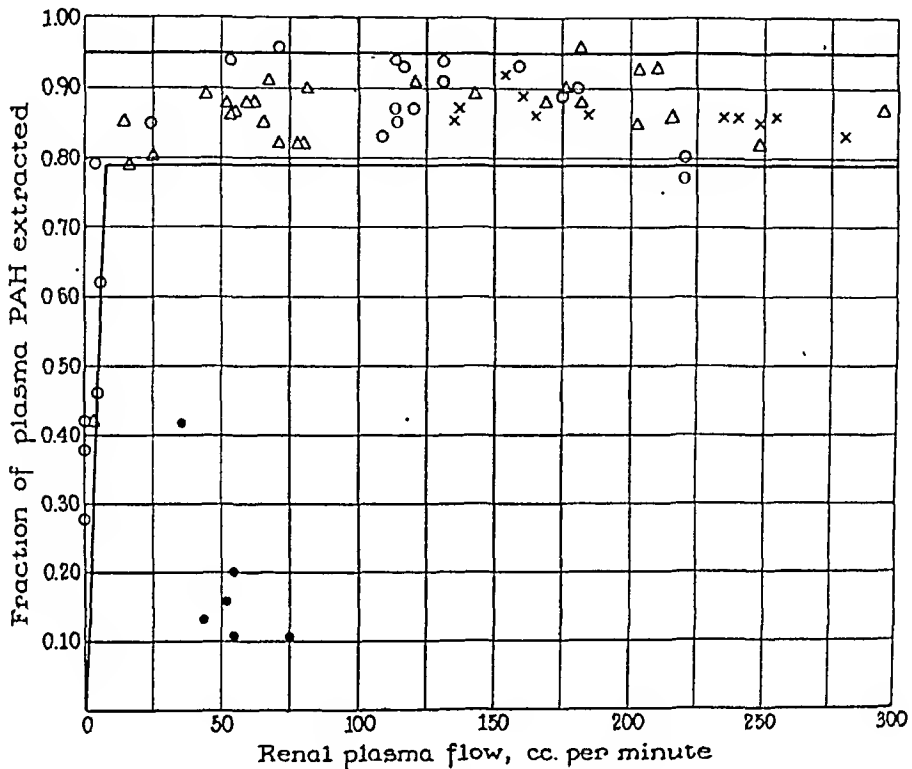


FIG. 1. Percentages of para-amino hippurate extracted from the plasma of the renal blood by the kidneys of dogs, in which the renal blood flow was either normal or diminished by conditions indicated by symbols as follows:

- × Normal dogs.
- Δ Dogs immediately after loss of varying amounts of blood.
- Dogs during traumatic shock of varying degrees.
- Dogs immediately after clamping the renal artery for two hours and then removing the clamp.

In each dog one kidney had previously been removed, and the observations were made on the functions of the remaining kidney. Renal plasma flows are not estimated from clearances, but are measured values calculated as (PAH excreted per minute)/(PAH extracted from 1 c.c. of renal plasma).

The results show that hemorrhagic or traumatic shock did not decrease the completeness with which the kidneys extracted PAH from the renal plasma until shock became so severe that the renal plasma (and blood) flow fell below 5 per cent of normal.

After temporary renal ischemia caused by clamping the renal artery for two hours, although removal of the clamp was at once followed by restoration of blood flow to about 50 per cent of pre-operative, the PAH extraction was only 10 to 20 per cent, about as much as would be filtered in the glomeruli, indicating that the tubules had nearly or quite ceased extracting PAH from the renal plasma. (Reprinted by permission from the American Journal of Physiology.)

The completeness of PAH extraction in the acute first phase of hemorrhagic shock (upper part of figure 1) can be explained by assuming that when the renal blood flow is decreased by hemorrhage or trauma the flow is completely shut off from part of the nephrons, while those that continue to be perfused continue to function in a normal way.

This assumption also could explain the observation²³ that during this phase of shock there is no significant decrease in the oxygen saturation of the renal venous blood. In contrast, in the body as a whole when the circulation rate is decreased the tissues compensate for the retarded blood flow by extracting a larger part of the oxygen from the blood, so that the venous blood, from the right heart, becomes dark and shows an increased degree of oxygen unsaturation.²³ In the kidneys, on the contrary, the blood flow can be reduced by hemorrhagic or traumatic shock without causing the renal venous blood to lose its normal, nearly arterial degree of redness or lower its oxygen content.²³ This also would be explainable if the diminished volume of renal blood passes through a proportionally diminished area of renal tissue at a normal rate, the rest of the kidney receiving relatively little blood.

After the kidney has suffered prolonged ischemia and reached the second phase of shock kidney, where restoration of the general circulation does not restore normal renal function, the incompleteness with which hippurate is extracted (points marked ● in figure 1) indicates decreased efficiency of the tubule. A possible explanation of this phase is that suggested by Trueta,⁴

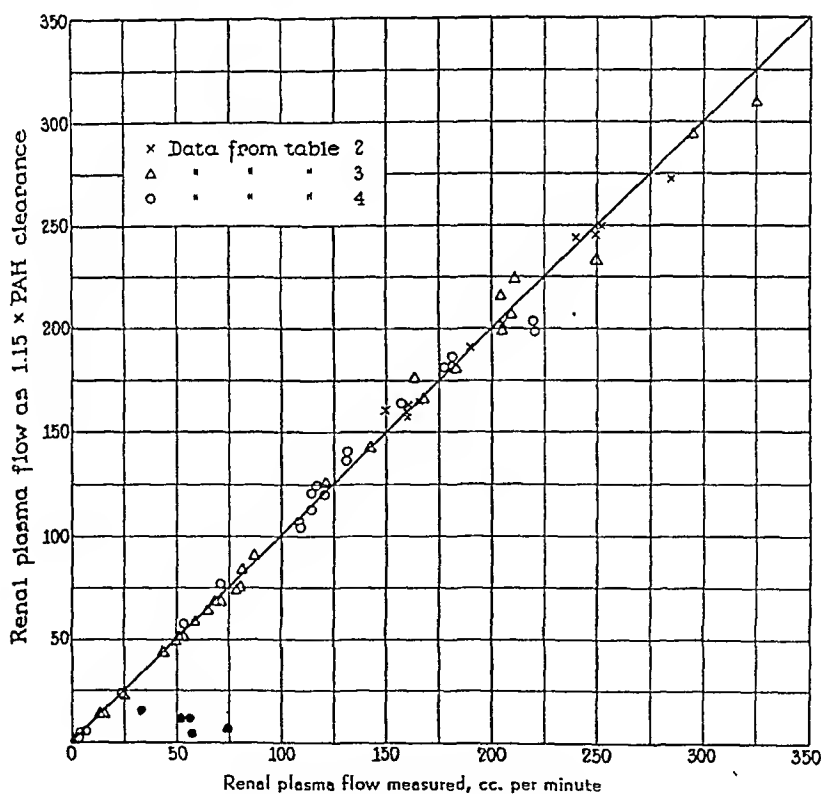


FIG. 2. Relation of renal plasma flows estimated as 1.15 times PAH plasma clearance to actual renal plasma flows measured as (PAH excreted per minute)/(PAH extracted from 1 c.c. of renal plasma). Symbols same as in figure 1.

The results show that in acute hemorrhagic or traumatic shock the PAH clearance serves as a measure of the renal blood flow, but that after the kidneys are injured by ischemia from 2 hour clamping of the renal artery the PAH clearance does not serve as a measure of the renal blood flow. (Reprinted by permission from the American Journal of Physiology.)

that the renal blood flow is diverted from the cortex to the medulla, where the nephrons apparently function less efficiently. But the explanation that seems at present more probable is that, as believed by Lucké, the tubular cells of the nephrons are damaged by the ischemia.

The data of figure 1, in addition to their significance concerning the effect of shock on the kidney, indicate that during the acute first phase of shock kidney, the plasma clearance of para-amino hippurate serves as a measure of the volume of blood plasma that perfuses the kidneys per minute. (The PAH clearance is the volume of plasma, the PAH content of which is excreted per minute. It is calculated as (PAH excreted per minute)/(PAH in 1 c.c. of arterial plasma).) If extraction of PAH were 100 per cent complete, the PAH clearance would exactly equal the renal plasma flow. When the extraction is 87 per cent complete, the renal plasma flow is the clearance multiplied by $1/0.87$, or 1.15.

When, however, the kidneys have suffered a period of ischemia so severe and prolonged that the tubules are damaged (second phase of shock kidney) the PAH plasma clearance no longer serves as a measure of renal plasma flow. The close relation of PAH clearance to renal plasma flow in the first

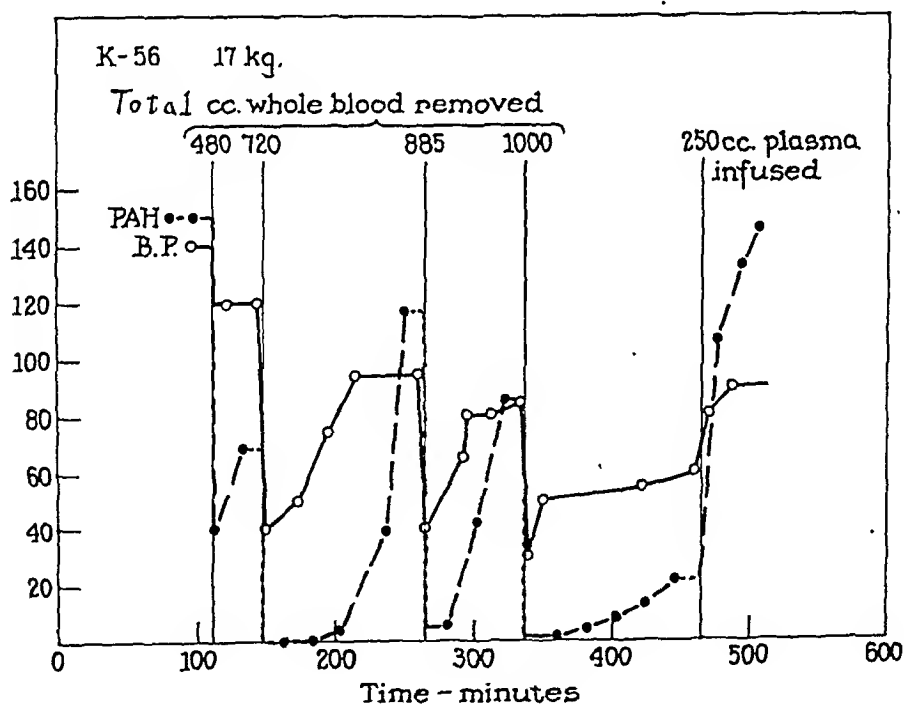


FIG. 3. Reversible shock. The effects of four successive hemorrhages on the blood pressure and the para-amino hippurate plasma clearance (PAH curve). Under the conditions of this experiment the PAH clearance serves as a measure of the renal plasma flow (figures 1 and 2).

The results show repeated recovery of blood pressure and renal blood flow (PAH curve) after repeated hemorrhages, the recoveries being attributable to shrinkage of the extra-renal vascular bed by peripheral constriction. The effectiveness of the relatively small plasma infusion in restoring general blood pressure and renal blood flow at the end of the experiment appears attributable to the continued maintenance of peripheral constriction. The shock had not become irreversible. (Reprinted by permission from the American Journal of Physiology.)

phase of shock kidney, and the absence of relation in the second phase, are indicated by figure 2.

Acute Hemorrhagic Shock Reversible with Respect to Both Renal Function and Circulation. In figure 3 are shown the effects of four successive quick hemorrhages during three hours on the arterial blood pressure and on the para-amino hippurate clearance of a dog. (Since the condition is acute reversible shock, PAH clearance may be assumed to indicate approximately renal plasma flow.) Each hemorrhage caused an immediate reduction in both blood pressure and hippurate clearance (PAH curve), but after each of the first three bleedings there quickly followed a rise both in arterial blood pressure and in the PAH clearance (renal plasma flow). After a fourth hemorrhage restoration of the PAH clearance was incomplete, but infusion of a volume of plasma equal to only one-fourth of the blood that had been withdrawn restored the clearance to practically normal.

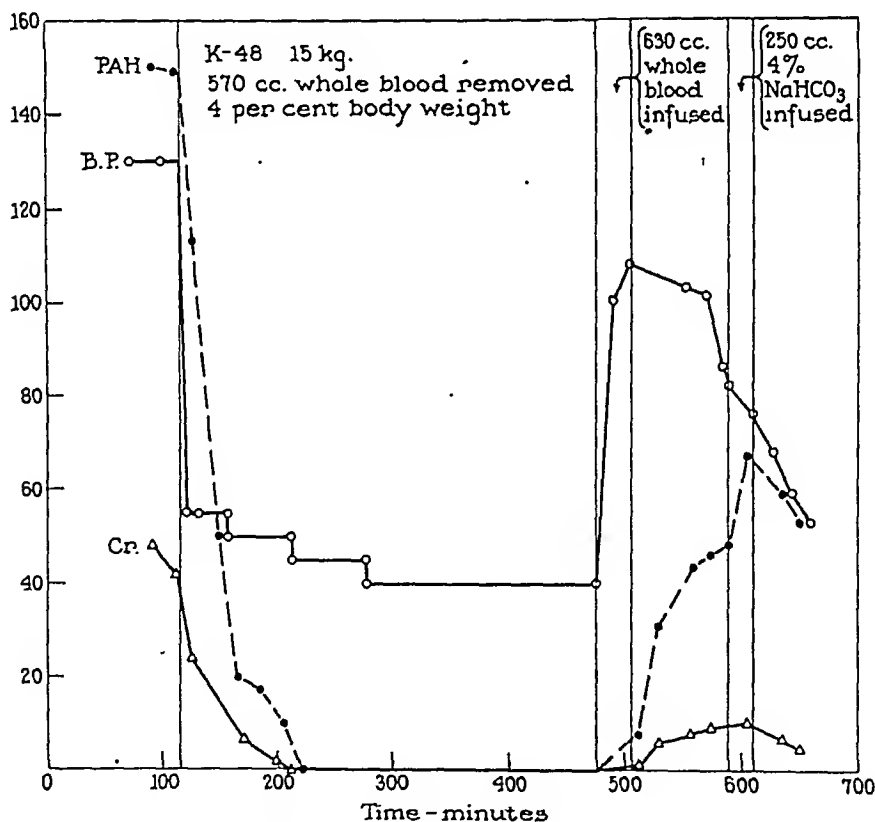


FIG. 4. Acute hemorrhagic shock reversible with respect to renal function but irreversible with respect to general circulation. PAH indicates para-amino hippurate clearance, B. P. blood pressure, Cr creatinine clearance (glomerular filtration rate in c.c. per minute). Although the blood withdrawn was less than in the experiment of figure 3, restoration of even more than the volume of whole blood withdrawn caused in this case only a temporary rise in blood pressure and in renal function. It appears that peripheral constriction had been replaced by dilation before the blood infusion was given. From ³. The quick transitory rise in PAH and creatinine clearances after the infusion indicates that the kidneys were still capable of functioning.

The apparent explanation of these phenomena is that immediately after a sudden hemorrhage the kidney shares with the peripheral circulation a decrease in blood flow, but that within a period, which may be only a few minutes, constriction of the extra-renal peripheral circulation sets in, blood pressure rises, and the circulation of the kidney is more or less completely restored. Presumably this peripheral constriction is caused by a vasoconstrictor substance shown to be present in the blood during shock^{24, 25, 26, 27, 28, 29, 30, 31}; apparently either the vasoconstrictor substance or its precursor is formed in the kidney.

Acute Hemorrhagic Shock Reversible with Respect to Renal Function but Irreversible with Respect to General Circulation. Figure 4 shows an experiment in which successive bleedings followed each other so rapidly that the effects of compensatory peripheral constriction in restoring renal function, seen in figure 1, did not appear. After five hours in severe shock, with mean arterial blood pressure at 40 mm., infusion of a volume of blood equal to that withdrawn caused only temporary rise in blood pressure, followed by a rapid decline. It is apparent that this animal had reached the stage of shock in which peripheral vasoconstriction is replaced by vasodilation^{28, 29, 30, 31} and circulatory death can no longer be prevented by transfusions. The fact that during the temporary rise of blood pressure following the transfusion a partial restoration of renal function at once occurred, as shown by the hippurate and creatinine clearances, indicates that the nephrons were not yet too severely damaged to recover.

Analysis of the Effects of Acute Hemorrhagic Shock on Renal Function. In figure 5 are data which permit an analysis of the immediate effects of hemorrhage on different parts of the renal function. Blood was withdrawn from the dog in successive portions as indicated by the curve at the bottom of the figure. The renal plasma flow in c.c. per minute was determined by dividing the amount of para-amino hippurate excreted in the urine per minute by the amount removed from 1 c.c. of plasma during passage of the kidney, as measured by simultaneous analyses of the plasma of arterial and renal venous blood. Creatinine clearances were determined and interpreted as measures of the filtration rate in terms of volume of glomerular filtrate formed per minute, since such interpretation appears valid during the first phase of shock. Dividing the filtration rate by the plasma flow gives the fraction of water in the plasma that is filtered during passage of the glomerulus. This "filtered fraction" is normally about 20 ± 5 per cent of the plasma water.²¹

Renal plasma flow underwent a progressive fall after withdrawal of the first 25 c.c. of blood per kilo. (Total blood volume in the dog is about 90 to 100 c.c. per kilo.) The arterial blood pressure, however, was maintained until the withdrawal exceeded 40 c.c. per kilo; it is evident that during this period peripheral constriction served to keep up the general arterial blood pressure. The fall in renal plasma flow after 25 c.c. of blood per kilo were withdrawn showed that from this point vascular constriction included the

kidney as well as peripheral tissues. A compensatory effect in maintaining renal excretory function is seen in the marked increase in the percentage of plasma water filtered in the glomerulus. This rose from 26 per cent to 38 per cent during the first four hours of the experiment. After this period

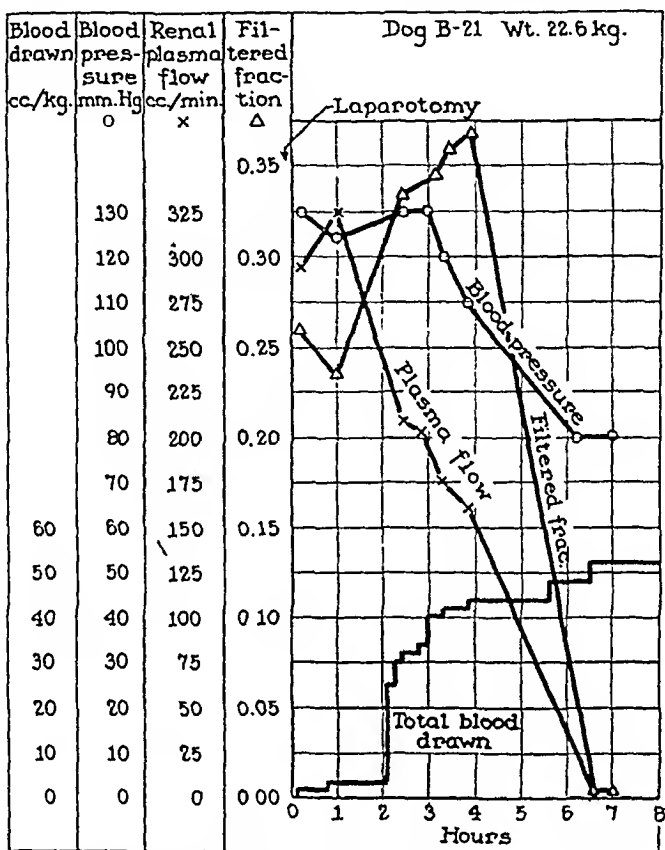


FIG. 5. Effects of gradual blood withdrawal on blood pressure, renal plasma flow, and the fraction of plasma water filtered in the glomeruli. The renal plasma flow fell steadily as amounts of blood over 25 c.c. per kilo were withdrawn, but the effect of the retarded flow on creatinine excretion was for three hours partly compensated by the increase in the filtered fraction of the plasma, presumably achieved by constriction of the efferent renal arterioles. When the volume of blood withdrawn exceeded 48 c.c. per kilo, renal blood flow and renal excretion fell to nearly zero. Since blood pressure in the femoral artery was still 80 mm., it appears that the final shutdown of the kidneys was attributable to constriction of the renal artery or its branches. The renal plasma flows were measured as (PAH excreted per minute)/(PAH extracted from 1 c.c. of renal plasma). The "PAH extracted from 1 c.c. of renal plasma" was measured directly by analyses of PAH in arterial plasma and in plasma of renal venous blood, the difference being the amount extracted from the plasma by the kidneys. This method of measuring renal plasma flow does not depend on any assumptions concerning the completeness of PAH extraction, or the mechanism by which PAH is excreted. (Reprinted by permission from the American Journal of Physiology.)

there was a rapid fall in both renal plasma flow and in the filtered fraction, so that the excretory function of the kidney fell almost to zero. This debacle of the kidney occurred despite the fact that the general blood pressure (femoral artery) was still maintained at 80 mm.; cessation of renal blood flow and function was therefore apparently due chiefly to constriction of the renal artery or its branches.

The terminal stage of the experiment of figure 5 illustrates the manner in which, when loss of blood volume is sufficiently severe to demand a maximal peripheral constriction in order to maintain blood pressure and blood flow through the heart and brain, the blood flow to the kidney is shut off along with the flow to the skin and skeletal muscles, and the function of the kidney is suppressed.

After-effects of Renal Ischemia Produced by Temporary Clamping of the Renal Artery. The kidneys of the dog have been shown to stand complete occlusion of the renal artery by clamping it for as long as three, and sometimes four, hours without irreversible damage.²⁰ After ischemia exceeding four hours, however, the damage was practically always irreversible and the animal died later in uremia without return of renal function.²⁰ In figure 6 is shown the slow recovery of renal function, as measured by the urea clearance, after two hours' clamping of the renal artery. Figure 7 shows the effects of ischemia prolonged for three hours; renal function, although not entirely abolished, did not recover sufficiently to prevent ultimate uremia.

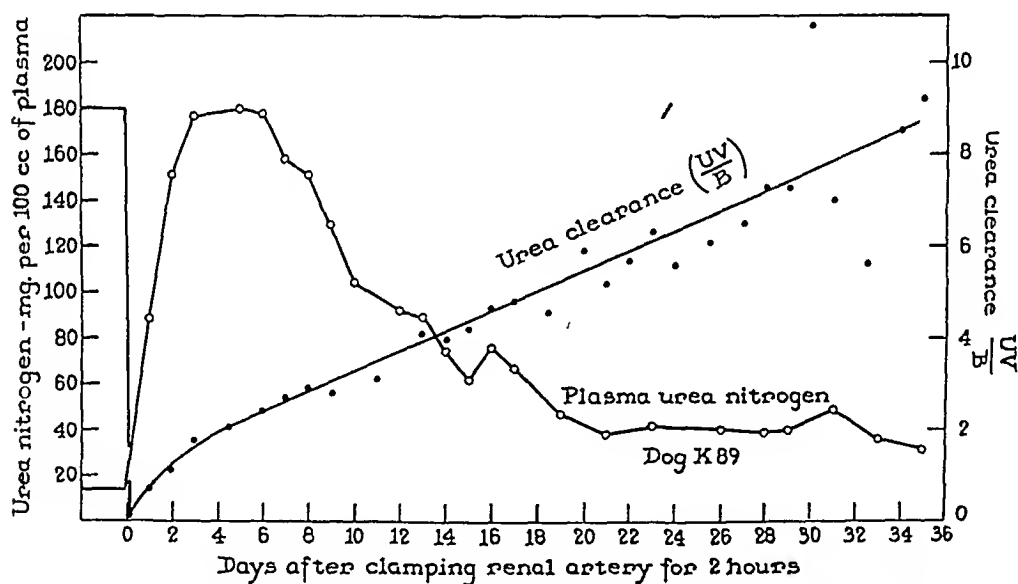


FIG. 6. Slow recovery from the effects of clamping the renal artery of the left kidney of a dog for two hours, the right kidney having previously been excised. After 34 days the plasma urea clearance reached its pre-operative level of 8 to 9 c.c. per minute. It will be noted that during the first four days urea was accumulating in the blood plasma, although the renal function, indicated by the urea clearance, was improving. It was only after the clearance had passed 2 c.c. per minute that the blood urea reached a plateau and then began to fall. (Reprinted by permission from the American Journal of Physiology.)

The renal damage caused by clamping the renal artery was more severe in the dog than the effect of hemorrhage sufficient to reduce the renal blood flow for the same length of time to so slow a rate that it could not be measured by the method employed. It was possible, as shown in figure 3, to depress the renal blood flow to nearly zero by hemorrhage for as long as three hours, and then obtain almost immediate return of function by restoration of the lost blood. It is probable that during the depression caused by

hemorrhage some small trickle of blood continued to get through the kidneys, so that the nephrons were not damaged as rapidly as by complete closure of the renal artery. It appears to be more difficult to produce post-shock uremia in the dog than in man. The apparent reason is that in the dog the kidneys, relatively to the circulatory system or other vital organs, are more resistant

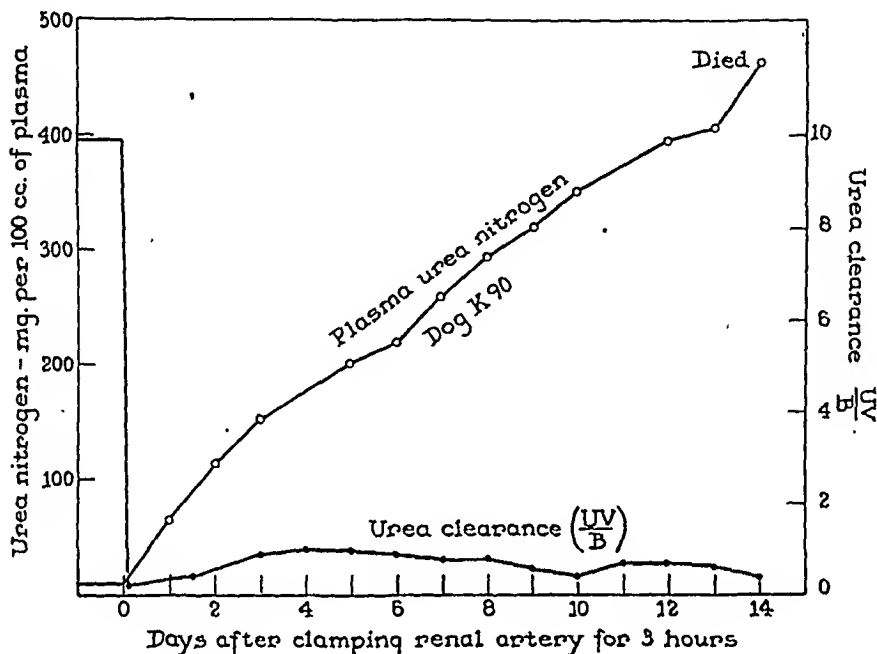


FIG. 7. Irreversible effects of renal ischemia caused by clamping the left renal artery of a dog for three hours, the right kidney having previously been excised. The slight increase in urea clearance observed during the first three days was not maintained, and was afterwards followed by a decrease, with death in uremia 14 days after the clamping. (Reprinted by permission from the American Journal of Physiology.)

than in man. Attempts to employ traumatic or hemorrhagic shock sufficiently severe and prolonged to cause irreversible renal failure in the dog caused acute death from circulatory failure (e.g. figure 4).

TREATMENT DURING SHOCK TO PREVENT RENAL DAMAGE

During acute shock, the renal damage caused by ischemia increases with its duration. Hence *the first move to forestall subsequent uremia is to cut the period of shock as short as possible by restoration of blood volume by rapid infusions, of saline solution in dehydration, or of saline, plasma or whole blood as needed after dehydration, burns, trauma, hemorrhage, etc.** Restoration of a flow of 1 c.c. of urine per minute containing 2 gm. or more of NaCl per liter serves as one indication of adequate fluid infusion^{32, 33} provided the renal damage phase of shock kidney has not been reached.

However, the practice of continuing infusion until a normal flow of urine is reestablished can not be blindly followed. When the renal damage phase

* However, when signs of shock are due primarily, not to factors causing loss of blood or fluid, but to cardiac failure, fluid infusion is obviously not indicated.

of shock kidney has been reached, anuria or oliguria may continue even after the patient is overhydrated, because the kidneys are incapable of resuming excretion. *Continuance of the infusion can then cause fatal cardiac or pulmonary embarrassment. Overadministration of fluids can be as dangerous as shock.* Criteria other than urine flow must be used, in cases with kidneys already damaged by shock, to indicate when enough fluid has been infused. Onset of pulmonary or subcutaneous edema warns that infusion has been overdone. Observations of the blood composition before and during infusion help to forestall such over-administration. When the cause of shock is dehydration, as in cholera, or loss of plasma, as in burns, blood specific gravity is high, and its return to normal during infusion of saline solution or plasma serves as a criterion of adequate infusion. Use of the blood specific gravity as a criterion was applied in Rogers' ¹⁶ classic work on cholera, and in Reimann's ³⁴ modern treatment. The easily handled copper sulfate method ³⁵ for blood and plasma specific gravity, which permits estimating the concentrations of both the plasma protein and the blood hemoglobin in a few minutes, has proved particularly practical in shock treatment.

When acidosis is present (as it is in most forms of severe shock except that caused by loss of gastric juice), the work of Sellards ³⁶ and Rogers ¹⁶ with cholera shows that administration of adequate amounts of bicarbonate can diminish the incidence of post-shock uremia.* The presence of severe acidosis appears either to accelerate renal damage during shock, or to retard subsequent repair of the damage. The amounts of bicarbonate required for correction of acidosis, according to the plasma CO_2 and the size of the subject are indicated by the line chart of figure 8.† For alkali therapy during acute shock, sodium bicarbonate is preferable to sodium lactate. The lactate does not act as alkali until the lactate anion is burned, and oxidation is likely to be retarded in shock, so that lactic acid is not oxidized; in fact the acidosis of acute shock appears to be partly due to failure to oxidize the endogenous lactic acid produced by the body. In prolonged post-shock renal failure, acidosis may develop, as in nephritis, from failure to form ammonia and to excrete acid products.

Correction of acidosis, besides its effect in decreasing the incidence of post-shock uremia, ¹⁶ appears to have an immediately beneficial effect on renal

* That acidosis also plays a part in the damage, presumably extra-renal, that causes death in acute shock, and that alkali therapy can decrease the mortality is shown by Wiggers and Ingraham.³⁷

† The line chart is calculated from data of Palmer and Van Slyke.³⁸

Bywaters ¹³ recommends as first step in treatment of crush injury, giving NaHCO_3 4 gm. per hour, by mouth if the subject is not nauseated, otherwise by vein, until the urine is alkaline, and giving about 30 gm. per day for the next two days to keep the urine alkaline. Such a procedure, based on urinary pH, may be followed when it is not feasible to determine plasma CO_2 . However, administering alkali until the urine turns alkaline may lead to over-administration. Darmady ⁹ found that shock falls within the group of conditions, usually marked by dehydration and salt deficit, in which the urine may fail to turn alkaline when plasma bicarbonate exceeds the normal limits. Experimental studies of this paradoxical concurrence of internal alkalosis and acid urine under conditions of dehydration and salt deficit in dogs and men have recently been published by K. K. Van Slyke and E. I. Evans.³² Darmady ⁹ found that determinations of plasma chloride as well as CO_2 were essential in guiding fluid replacement in shock since chloride depletion was frequent.

function. We have seen anuria, persisting after adequate saline infusion, relieved at once when sufficient bicarbonate was infused to relieve the acidosis.

When shock is due to dehydration with loss of body salts, as in diabetes and cholera, and great volumes of saline infusion are required, it

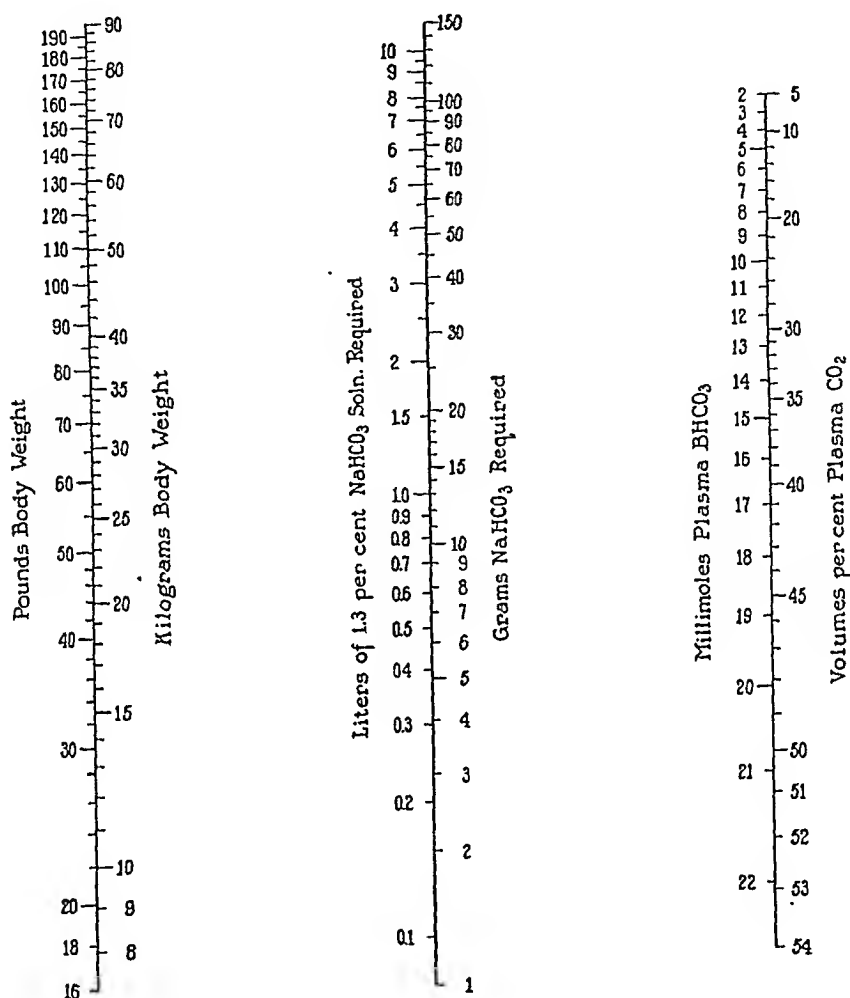


FIG. 8. Line-chart showing amounts of sodium bicarbonate required to overcome acidosis of varying degree. A straight line drawn from the point on the right hand scale indicating the subject's plasma CO₂ or HCO₃ content to the point on the left scale indicating his body weight cuts the middle scale at a point showing the amount of NaHCO₃ required to restore the plasma CO₂ to a normal value of 60 volumes per cent or 27 millimoles per liter. The chart is based on the finding of Palmer and Van Slyke³⁸ that 0.026 gm. of NaHCO₃ per kilo body weight is required to raise the plasma CO₂ by 1 volume per cent.

appears safer to include K, Ca, and Mg in the infusions, rather than only NaCl and NaHCO₃. One cannot use Ca and NaHCO₃ in the same solution, as the slight amount of Na₂CO₃ that is formed, in the equilibria, $\text{H}_2\text{CO}_3 \rightleftharpoons \text{NaHCO}_3 \rightleftharpoons \text{Na}_2\text{CO}_3$, suffices to precipitate CaCO₃. Calcium can be infused separately as CaCl₂, as was done by Rogers¹⁰ in treating cholera, or as gluconate. That plasma potassium deficit may become sufficient to

cause dangerous symptoms in patients treated for diabetic acidosis has been shown by Martin and Werkman.³⁹ Van Slyke and Evans^{32, 33} found marked decrease of plasma potassium also in dogs that were dehydrated by loss of gastric juice, and then rapidly rehydrated by NaCl infusions. Hartmann⁴⁰ uses a balanced solution containing, per liter, 6 gm. of NaCl, 4 gm. of sodium lactate, 0.4 gm. of KCl, 0.2 gm. of $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, and 0.2 gm. of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$. This does not contain enough alkali (lactate) to treat severe acidosis, but appears safer than "physiological" 0.9 per cent NaCl solution, which is really unphysiological, for routine infusion.

TREATMENT AFTER SHOCK TO PREVENT UREMIA

When, after recovery from the general effects of shock, anuria persists, or the urine specific gravity remains low in comparison with the volume output and blood urea shows a steady rise, one has to deal with persisting renal damage. The objects of treatment during this stage are (1) to provide optimal conditions for renal recovery, and (2) to minimize the accumulation of excretory products, in order that onset of uremia may be retarded, and that thereby life may be prolonged to give the kidneys as much time as possible to recover. Recovery of renal function may occur after several days of anuria in this stage.

Maintenance of normal plasma bicarbonate and chloride concentrations appears to favor recovery of the kidneys. A high-calorie diet consisting chiefly of fats and carbohydrates, and low in protein,⁴¹ minimizes the formation of nitrogenous products of catabolism, and also the acid products, phosphoric and sulfuric acids. A diet of rice and butter has been found satisfactory.⁴¹ It also provides an intake low in potassium, the accumulation of which in the blood may reach a toxic level in renal failure. The low protein diet is indicated only as long as deficient renal function persists. The depletion of blood and tissue proteins, which frequently accompanies or follows the conditions that produce shock, indicates change to a generous protein diet as soon as renal function is restored.

Kolff^{42, 43} has shown that the accumulation of toxic products, either organic or inorganic, during renal failure can be prevented by vivodialysis with the "artificial kidney," which was devised by Abel⁴⁴ and developed for clinical application by Kolff.^{42, 43} Blood from an artery is passed through a long cellophane tube bathed in a solution containing NaCl, NaHCO_3 , KCl, and glucose, and then returned to a vein. Kolff⁴¹ has seen recovery of normal kidney function in a case that had suffered post-shock anuria for two weeks, during which uremia was prevented by vividiffusion. Experiments by Fine, Frank, and Seligman⁴⁵ indicate that similar results may be obtainable by peritoneal irrigation, although the danger of peritonitis appears serious.

Throughout the post-shock period of depressed renal action, it is essential to guard against overhydration, since the ability of the kidneys to excrete

salt and water may be limited. Observing blood and plasma protein concentrations by such means as specific gravity measurements³⁵ assists in detecting overhydration before its unfavorable effects become serious.

SUMMARY

An immediate effect of shock from hemorrhage, trauma, or dehydration is a decrease in renal blood flow and function, which may lead to complete anuria. Compensatory constriction of non-renal peripheral vessels follows, and if the loss of circulating blood volume has not been too severe, renal blood flow and function may be quickly restored.

If shock is sufficiently severe, the kidney is included in the peripheral constriction. Renal constriction and anuria in this phase may continue even when the arterial blood pressure is as high as 100 millimeters.

The above phenomena accompany the first, or circulatory, phase of the shock kidney. If renal ischemia does not continue too long even severe shock does not damage the renal cells, and restoration of renal function quickly follows restoration of the general circulation.

If, however, severe renal ischemia continues for a sufficient number of hours, the second, or renal damage phase, of shock kidney develops. The kidneys are damaged, so that restoration of the general circulation no longer causes rapid restoration of renal function. The most obvious visible damage is located in the cells of the loop of Henle and the distal tubules, and tubular reabsorption of excretory products from the glomerular filtrate appears to be the most probable cause of renal failure in this phase.

If the renal damage is not too severe gradual recovery of the kidneys may occur, so that even after several days of post-shock anuria the renal function may improve sufficiently to prevent uremia, and recovery may eventually become complete. In fatal cases anuria or inadequate excretion persists, and death in uremia occurs in a period that may vary from two to 20 days.

To diminish the danger of death from post-shock uremia, certain precautions appear to be indicated: (1) Cut the duration of shock as short as possible by quick restoration of blood volume through adequate replacement of lost blood, plasma, or saline solution. (2) If acidosis is present, either during or after shock, administer adequate amounts of bicarbonate. (3) While administration of large amounts of fluid may be necessary to obtain normal blood volume and hydration, overadministration is to be avoided both during and after shock, or circulatory embarrassment may be caused. Measuring blood and plasma specific gravities is of practical assistance in planning and guiding fluid administration. (4) When, after recovery from acute shock, anuria or excretion of urine of low volume and specific gravity persists, and blood urea continues to mount, give a diet high in carbohydrates and fat, and low in protein, to retard accumulation of catabolic products. (5) It appears also that vividiffusion or peritoneal irrigation may retard onset of uremia and increase the opportunity for recovery of renal function.

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STUDIES ON THE CIRCULATION WITH THE AID OF TAGGED ERYTHROCYTES IN A CASE OF ORTHOSTATIC HYPOTENSION (ASYMPATHICOTONIC HYPOTENSION) *

By G. NYLIN and M. LEVANDER, Second Medical Clinic, Sabbatsberg's, Hospital, *Stockholm, Sweden*

MAN has established his superiority over the other animals by assuming the erect posture, but he has to pay the price in the form of certain diseases which include orthostatic defects of the circulation. An interesting case of this kind has recently come under our care, and we wish to report on the studies we have been led to undertake on this account.

Before one can understand the orthostatic diseases, it is necessary to be acquainted with the normal regulatory mechanism which comes into operation when a person assumes the erect posture after lying down.

The immediate result of this change of position is an increase in the hydrostatic pressure in the lower limbs. If the vascular system consisted merely of elastic, independent tubes, the increase in pressure would cause a considerable expansion of the venous part of the system. The venous pressure would rise, in proportion to the height of the column of blood, to values which would damage the capillaries, and the flow of blood to the periphery would reduce the return and cause fluctuations in the circulation. This does not normally occur, as the following experiments on leg volume and venous pressure show.

The volume of the lower extremities increases, it is true, in the erect position but, particularly in persons in good training, the increase is very slight (Asmussen³ et al.). The increase in volume is both intra- and extra-vascular, being occasioned both by blood and by tissue fluid. The first increase in volume is probably intravascular; the loss of plasma from the capillaries as a result of the increased filtration pressure (estimated by Thompson et al.⁵¹ at about 10 per cent of the volume of blood in circulation) can scarcely take effect at once, just as it is 20 to 30 minutes before reabsorption is complete (same writers). Levin³³ also claims to have shown that in the erect position the volume of the blood decreases and the hemoglobin percentage rises. *The venous pressure* in the lower extremities does not increase in proportion to the height of the column of blood (L. Hill quoting Starling, and Grill (1937) quoting Warburg) as it should if purely physical laws were operating, and if the valves were not functioning.

The maintenance of the circulation in the erect posture is rendered possible by the extensive regulatory mechanism which the body has at its command, and, which operates in various fields in accordance with the table below.

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TABLE I

Operative Factors in the Adjustment of the Circulation to the Erect Posture

- A. On the venous side to counteract an increase in volume and pressure.
 - 1. The pumping action of the muscles.
 - 2. Vasoconstriction.
 - 3. The pressure of the tissues.
- B. On the arterial side to counteract the flow of blood to the periphery.
 - 1. Vasoconstriction with
 - a. Transfer of blood to reservoirs.
 - b. Decrease in the volume of the arterial bed.
 - 2. Acceleration of the pulse.
- C. More efficient use of the blood at the periphery.
 - 1. Increase in the arteriovenous oxygen difference.

N.B.: The factors which operate on the venous side tend in various ways to reduce the pooling of the blood as much as possible.

A. 1. *The pumping action of the muscles* is due to the fact that muscular contraction causes compression of the veins which, owing to the valves in the latter, results in a flow of blood towards the heart. The importance of this factor is shown by the following experiments which Asmussen³ has carried out. The significance of the minor contractions which take place in standing still is shown by a comparison between the flow of blood to the legs when the subject actively assumes the erect posture and when he is tipped passively to an angle of 60° from the horizontal plane; in the latter case the flow is greater because the muscles are relaxed, despite the fact that the hydrostatic pressure is less. In two other subjects, the volume of the legs was no greater when they were working in the erect posture than when they were resting in the recumbent position. The dilatation of the muscle capillaries must, therefore, have been accompanied by a corresponding decrease in volume on the venous side resulting from increased muscular pumping. When the latter ceased with the stoppage of work, a considerable increase in volume occurred at once, presumably aggravated by the persisting capillary dilatation which delayed the emptying of the veins. Haxthausen (1932) and Beecher, Field and Krogh (1936) have shown that small movements of the foot can greatly reduce the venous pressure (quoting Warburg). The same writers suggest that arterial pulsation has the same effect as muscular contraction on the veins which lie in the vascular sheaths.

2. *Vasoconstriction.* The veins, like the arteries, are supplied with sympathetic vasoconstrictor nerve fibers which increase their tone. Very little is known about this mechanism, however. According to Heymans, it is regulated by the carotid sinus, the aortic body, the medulla oblongata and the hypothalamus. It seems natural to suppose that a vasomotor reflex plays an important part in the regulation of the venous, as well as of the arterial system.

3. *Pressure of the tissues.* This factor is hard to estimate but must be of considerable importance since it opposes the increase in the filtration pressure brought about by hydrostatic forces. The increase in diffusion of plasma into the tissues which occurs in the erect posture increases the tissue

pressure until equilibrium is established. The orthostatic disturbance which occurs after lying down appears to be due in part at least to a reduction of the tissue pressure.

B. The momentary fall of blood pressure which follows the assumption of the erect posture provides adequate stimulus for the pressure-sensitive regions in the carotid sinus and aortic arch. Impulses are emitted from there which bring about a reflex increase in sympathetic activity. This facilitates the adjustment of the circulation to the diminished return by the following compensatory mechanisms:

1. *Vasoconstriction.* On assumption of the erect posture, the vessels in certain areas contract and so bring about a rise in blood pressure which improves the circulation in other regions, e.g. the cerebrum.

The lungs appear to constitute one of the areas of vascular tissue which can contribute to this type of compensation. It has been known for a long time that the vital capacity is greater in the erect than in the recumbent position. Sjöstrand⁴⁷ has shown how the increase in the volume of the legs which occurred when two healthy persons stood up was accompanied by a corresponding increase in the vital capacity. The vital capacity, according to Sjöstrand and Jonsell, is closely connected with the amount of blood in the peripheral pulmonary vessels, and this suggests that the lungs can act as a form of blood reservoir. The word "reservoir" must be taken in its widest sense, i.e. to signify a vascular tissue which can assist in the transfer of blood from one part of the body to another. This particular reservoir is of especial significance in that it renders possible an interchange of blood between the systemic and the pulmonary circulations; an ingenious link in the regulatory chain, particularly as it can simultaneously increase the ventilatory capacity of the lungs.

2. *Acceleration of the pulse.* This reaction seeks to maintain the cardiac output despite the fall in the venous return.

Despite all the above compensatory reactions, there occurs often but not always (Grollman,²² Nylin³⁸) a fall in the cardiac output and a fall in the systolic blood pressure on assumption of the erect posture. The organism possesses, however, yet another regulatory mechanism:

C. *More efficient use of the capillary blood.* An indication of this is provided by the great increase in the arteriovenous oxygen difference which S. Weiss et al.⁵⁵ and Nylin³⁸ have demonstrated.

The operation of the regulatory mechanism can be observed in various ways. Thus, for instance, when a healthy individual stands up, the pulse rate increases by not more than 27 beats per minute within 3 to 5 minutes; the systolic blood pressure does not fall more than 20 mm. and the diastolic pressure rises slightly or falls not more than 5 mm. (Åkesson⁵⁶).

In contrast to the above, persons suffering from a failure of any part of the regulatory mechanism complain of certain symptoms when in the erect or raised posture. Since the brain is more sensitive than any other part of the body to oxygen lack, it is natural that the principal symptoms should

originate in that organ, and in fact exhaustion, vertigo, blurred vision, headache, lack of concentration and finally syncope may be experienced on standing. These subjective symptoms are not specific, however, but are common to all types of anemia of the brain. Diagnosis must therefore be based on the case history and on an objective examination of the circulatory mechanism; primarily, and most simply, on the blood pressure and the pulse. In this way it is possible to distinguish two essentially different types of orthostatic disorder or orthostatism.

In one group, there is an excessive pooling of the blood on the venous side of the vascular system below the heart; this condition is widely recognized. The disorder evidently concerns group A of the regulatory mechanism; the reflex mechanism, group B, is intact, however, and seeks to counteract the pooling by greatly increased sympathetic activity. The latter may lead to tachycardia and involves strong arteriolar constriction. The diastolic blood pressure is usually not only maintained but increased. Yet the cardiac output falls sharply and so do the systolic pressure and pulse pressure. The fluctuations in the circulation may lead to syncope. These cases can be classified as *sympathicotonic orthostatism*, and the other main group as *asymptothotonic orthostatism*. In the latter group, the essence of the malady is defective vasomotor response accompanied by an unvarying pulse and the absence of blood pressure regulation when the subject is tipped downwards.

Sympathicotonic orthostatism is by far the most common. The most important type is *arterial orthostatic anemia* (Bjure and Laurell); but this group also includes persons with a dilated venous bed (due to varices or venous angioma), convalescents, anemics and pregnant women. This orthostatism can be induced experimentally, e.g. by nitrites. Weiss et al.^{54, 55} have shown that the condition is due to a decrease in tone on the venous side of the vascular system, with an abnormal pooling of the blood on standing. Collapse occurs despite arteriolar constriction and tachycardia. We are therefore classifying this condition as *sympathicotonic orthostatism*.

A perfectly distinct type is the postural hypotension described by Bradbury and Egglestone⁷ in 1925—a disease of the vegetative nervous system. In typical cases, there is no acceleration of the pulse and a sharp fall in the systolic and diastolic pressures on standing. These cases are decidedly *asymptothotonic orthostatism*. The first case was observed in 1891, and was published by Laubry and Doumer³² in 1932. About 10 similar cases have since been published under various names, such as orthostatic hypotension and "l'hypotension artérielle orthostatique."^{1, 6, 10, 11, 12, 16, 17, 20, 21, 23, 27, 30, 31, 34, 37, 44, 46, 49, 54}

The nomenclature is somewhat confusing. Arterial anemia and a certain degree of hypotension certainly exists in all types of orthostatism. The simple names *sympathicotonic* and *asymptothotonic orthostatism*, which cover the essence of the subjective and objective symptoms, seem calculated to provide greater clarity both in differential diagnosis and in etiology.

Extensive operations on the sympathetic nervous system lead to ortho-

static hypotension (Hammarström,²⁴ MacLean and Allen,³⁵ Roth⁴⁵). This is fully explained by the loss of vasoconstrictor reflexes, which indeed, as for instance in cases of hypertonia, may have been the objective of the operation. Since the accelerator nerves are usually left intact, the pulse rate can still be increased, and this in fact occurs on standing, but there is a fall in both the systolic and diastolic blood pressures. An intermediate form of orthostatism, with a partially defective reflex mechanism, has thus been operatively induced. It might be termed *hyposympathicotonic* (or *semi-sympathicotonic*) *orthostatism*. A number of cases which have been reported as postural or orthostatic hypotension belong to this intermediate type.

Endocrine disorders, such as Addison's disease, and Simmonds' syndrome, may lead to orthostatic hypotension and a fall of systolic and diastolic blood pressures. The pulse is not unvarying, and the case almost corresponds to *hyposympathicotonic orthostatism*.

Asympathicotonic and *sympathicotonic orthostatism* differ only in degree and are therefore presented together in the following table.

TABLE II
The Authors' Table of Orthostatism

- A. Sympathicotonic.
 - 1. Arterial orthostatic anemia (Bjure and Laurell).
 - 2. Experimentally induced orthostatism.
 - 3. Varices and venous angioma.
 - 4. Pregnancy.
 - 5. Convalescence after lying in bed.
 - 6. Anemia.
- B. Asympathicotonic (hyposympathicotonic).
 - 1. Postural hypotension (Bradbury and Egglestone).
 - 2. A consequence of operations on the sympathetic nervous system.
 - 3. Endocrine disturbances.

We now wish to describe a case of pronounced asympathicotonic orthostatism.

SUMMARY OF CASE RECORD *

The patient was a 69 year old retired master painter, born in 1876. He enjoyed reasonably good health until his sixtieth year, when he started to suffer from vertigo. He was treated for this complaint at Örebro Hospital, where he was found to suffer from low blood pressure in the morning; systolic about 80 to 90, rising to 120 to 130 mm. in the afternoon. He subsequently consulted several doctors and was given various medicines without effect. His giddiness has been most pronounced in the mornings and after meals, and he has fainted several times. He feels weak and breathless when climbing stairs. In the evenings, however, he feels quite normal. When he stands erect he begins to feel uncomfortable, but after sitting down for a short time he recovers. If he stands on one leg and rests the other foot on a chair he can remain erect much longer than when he stands on both legs. He says that he never sweats. He consulted one of the authors (Nylin) in 1944, and a tonographic examination of the patient lying down and standing up showed him to be suffering from orthostatic hypotension. In 1945, he also began to suffer from tremors, mainly in the left arm and leg. They are most pronounced when he is resting, and he has to exert himself in order to relax.

* From the Second Medical Department; Sabbatsberg's Hospital.

General condition. (This has been unchanged, except for the condition of his nervous system, throughout the period in which he has been treated at the hospital, and so the following data are taken from examinations made on various occasions.) Fairly asthenic, thin. Height 171 cm., weight about 55 kg. Pale and dry skin. Mouth and pharynx: tongue not smooth, tonsils normal. Palpation of thyroid and lymph glands revealed no abnormality. Abdominal wall soft, but not tender. No resistance to palpation.

Circulatory system: No cyanosis or dyspnea in resting state. Radial arteries rigid. Heart: sounds normal. Pulse full and regular. Blood pressure: See figure 1. Venous pressure: (5/30/45) 6-7 mm. Circulation time (5/30/45) with MgSO_4 25-60-90 seconds (slightly prolonged).

Nervous system: (11/8/44). Pupils of equal size, round and reacting normally. Patellar reflex brisk and bilateral. Achilles reflex positive and bilateral. Babinski negative. No other comment. (6/7/45). *Cranial nerves:* I. Very reduced sense of smell. No other noticeable abnormalities in the cranial nerves. *Motor system:* Slight large-wave tremor on exertion, particularly in left arm and leg. *Reflexes:* Pupillary normal. Arm reflexes similar on both sides. Abdominal reflex absent (?). Cremaster normal and bilateral. Patellar and achilles perhaps slightly exaggerated. Downward Babinski on both sides. *Sensory system:* Rough tests revealed no abnormality. [10/26/45 (Prof. N. Antoni—extract).]

Psychological condition: Correct memory and normal orientation. Attention and concentration reduced. Test 100-3 slowly and with many mistakes. Repeats six figures. Mental arithmetic: Cannot manage more than multiplication table. Emotional state: affective reactions adequate. Expression: Fairly pronounced mask face. Speech and writing normal. *Cranial nerves:* 1. Smell—tested with petrol, eau de cologne, peppermint oil and camphor oil, the patient could identify only the first. He detected some smell from the other liquids but could not identify it. 2. Field of vision roughly tested appeared normal. Retina: Fine arteries of varying calibre; the veins are nicked at points, where they are crossed by arteries. Nerve heads normal. 3, 4 and 6. Position and movement of eyes normal. 5. No comment. 7. Right corner of mouth lower than left. In whistling, the orifice is drawn to the left. Right corner of mouth less mobile than left. No tremor. 8. No comment. 9, 10, 11 and 12. No comment.

General motility: Slight but unmistakable rigidity in the left arm. "Cog-wheel" phenomenon in left wrist and elbow joints. Strength: No definite reduction. Arms raised above the head: Left arm possibly slightly slower than right. Barre: faintly positive on left side. No fibrillar jerking. Posture normal. Hyperkinesia: Large-wave fairly rapid tremor in left arm and leg of typical Parkinson nature. No pathological synergic movements. Gait: No synergic movement of left arm, otherwise normal. Romberg negative. Diadochokinesia: left arm somewhat more resistant than right.

General sensitivity: No comment.

Reflexes: Pupils round, average diameter of equal size. Normal reaction to light. Near sight normal. Corneal and pharyngeal reflexes normal. Muscle reflexes: bilateral. No pathological reflexes. Abdominal reflexes absent. Cremaster reflex: bilateral. Babinski negative bilateral. Horner's syndrome absent. No thermosymmetry. Bladder and rectum normal.

Conclusion: Parkinson's disease, unilateral.

Laboratory tests: Hb. 63 to 72 per cent. Red blood cells 3.3 to 3.6 millions. Leukocytes normal. Sedimentation rate 5-11 mm./hr. Non-protein N 42 to 48 mg. per cent. Serum iron (10/26/45) 0.111 mg. per cent.

Urine: No albumin. Sediment: nothing pathological. Rate of excretion: Average for 10 days 990 c.c.—470 by day and 520 by night.

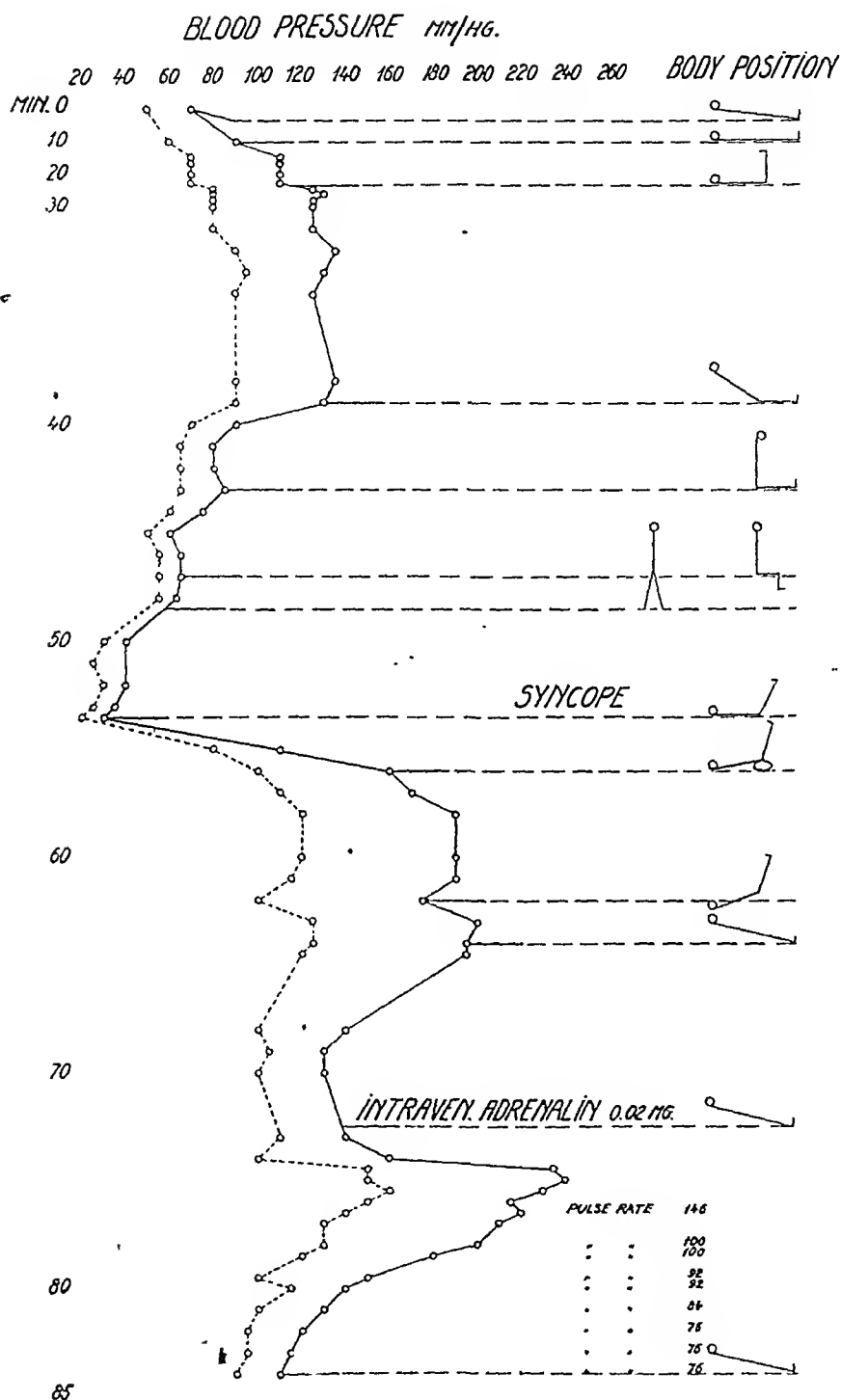


FIG. 1. The influence of various changes of posture on blood pressure in a typical case of postural asympathicotonic hypotension recorded for 85 minutes.

Renal function:

Creatinine clearance:	Head raised 25°	Head lowered-25°
7/6	138 c.c./min.	152 c.c./min.
12/6	120 c.c./min.	152 c.c./min.

Water test with one liter of water (figure 2):

Excretion during first 4 hrs.	Feet lowered	Head lowered
Maximum dilution	660 c.c.	1035 c.c.
	Spec. gravity 1.015	Spec. gravity 1.006

Blood sugar during a 24 hr. period varied between 91 and 108 mg. per cent. Wassermann, Kahn and Meinicke (II) tests in blood all negative.

X-ray examination: Skull and sella turcica (5/30/45 and 10/9/45): General views of the skull show no sign of damage to the cranium or other abnormalities. Sella turcica normal size and shape, nothing pathological can be observed. Behind the dorsum sellae, a stripe-like dense shadow can be seen where calcification has occurred at the attachment of the tentorium cerebelli. *Stomach and colon:* normal.

Basal metabolic rate: The BMR rises when the head of the bed is lowered to 25° below the horizontal. At the same time, the blood pressure rises to 175/100 mm. Hg (figure 2).

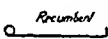
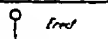

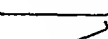
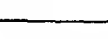
	Blood pressure mm/Hg	Pulse rate	Heart volume cc	Venous pressure CC	Circ. time sek.	Circulatory blood-co. pulse volume gr	Hematocrit %	Total circulatory blood volume ml	Oxygen consumption (C/min)	Blood sugar %	Non protein nitrogen	Filtration	Urinary secretion ml	Urin. sugar
 Recumbent	125/80	64	900	7	25	2380	34	6470		104				
 Erect	40/30		640			2065	34	5640						
 25°	60/45	66				1550	33	4700	166	109	32	133 120 112 H-123	660	1015 1022
 25°	175/100	66				1570	32	4910	184	101	33	168 152 129 H-133	1035	1006 1014
 45° Oxygen administered extremely	215/115	115				1700	32	5320						

FIG. 2. Observations upon the effects of changes in the patient's position.

Special studies on the circulation: Figure 1 shows that even very small changes in posture profoundly affect the blood pressure. The systolic blood pressure varies between the following extremes without being accompanied by any change in pulse rate: Horizontal position 90 mm. Hg; sitting 64 mm.; standing 30 mm. (syncope); horizontal with legs raised 160 mm.; same with head below horizontal level 200 mm. Hg. Administration of 0.02 mg. adrenalin raised the systolic blood pressure to 240 mm. Hg and the pulse rate to 146 per min.

The electrocardiogram is shown in figure 3. It is to be noted that there is no change in heart rate, in T-waves or in other respects in either standing or recumbent position, nor after hypoxemia tests.

Roentgen-ray of the heart (figure 4) shows that the heart decreases considerably in volume in the standing position, but not more so than occurs in normal individuals (Nylín³⁸). (Method devised by Liljestränd, Lysholm, Nylín and Zachrisson.³⁹)

The oscillogram made on November 9, 1944 (figure 5 A), indicates that when the patient is lying down, the blood pressure in the upper limbs is 160/105. On standing,

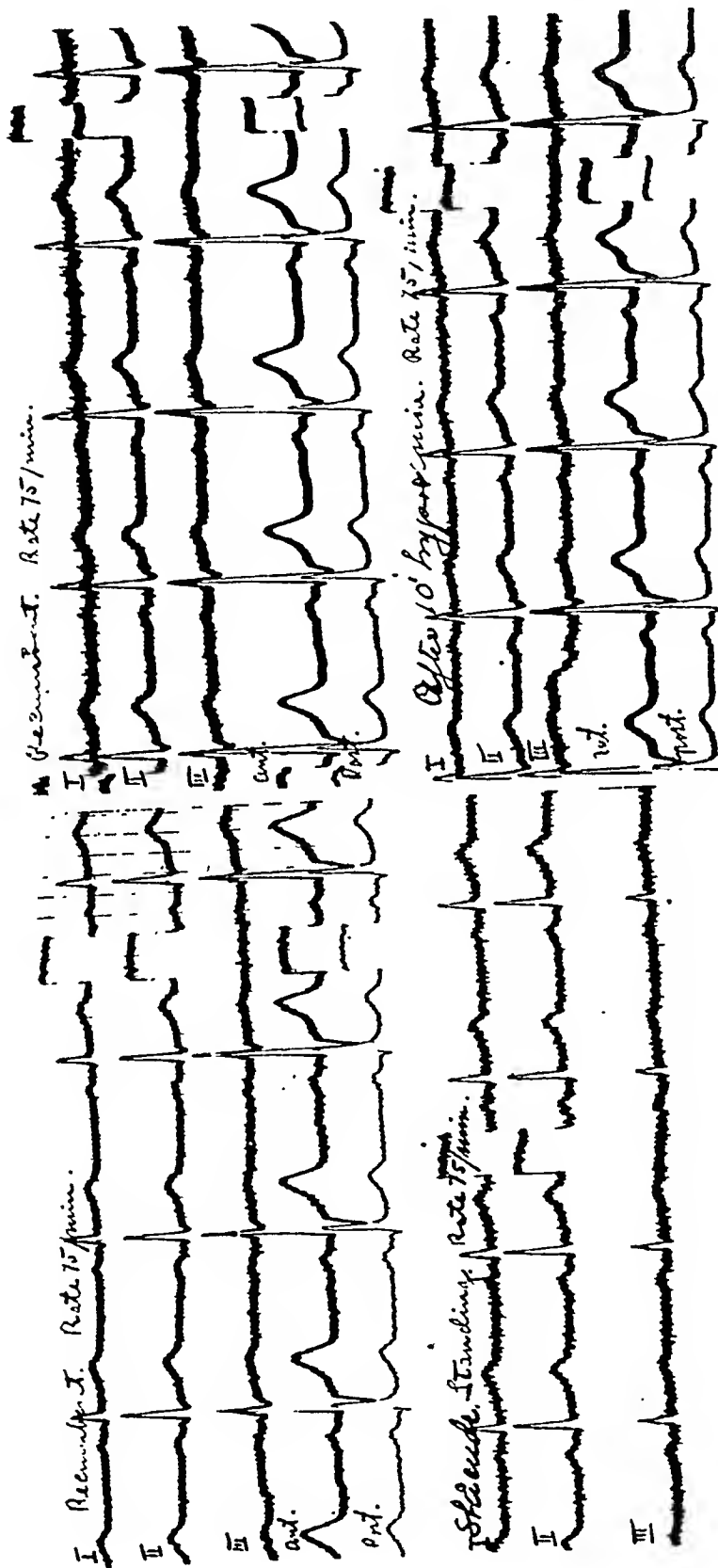


FIG. 3. Electrocardiograms taken with the patient in various positions.

both the systolic and diastolic pressures fall, and the only way to maintain the patient in this position without his fainting is by letting him place one foot on a chair. The blood pressure falls to 70/60, but rises again to its original level when the patient lies down. There is no acceleration of the pulse in the erect posture.

An oscillogram was made about a year later, October 11, 1945 (figure 5 B). The patient is lying in bed, and the whole bed is tipped as shown. The blood pressure in

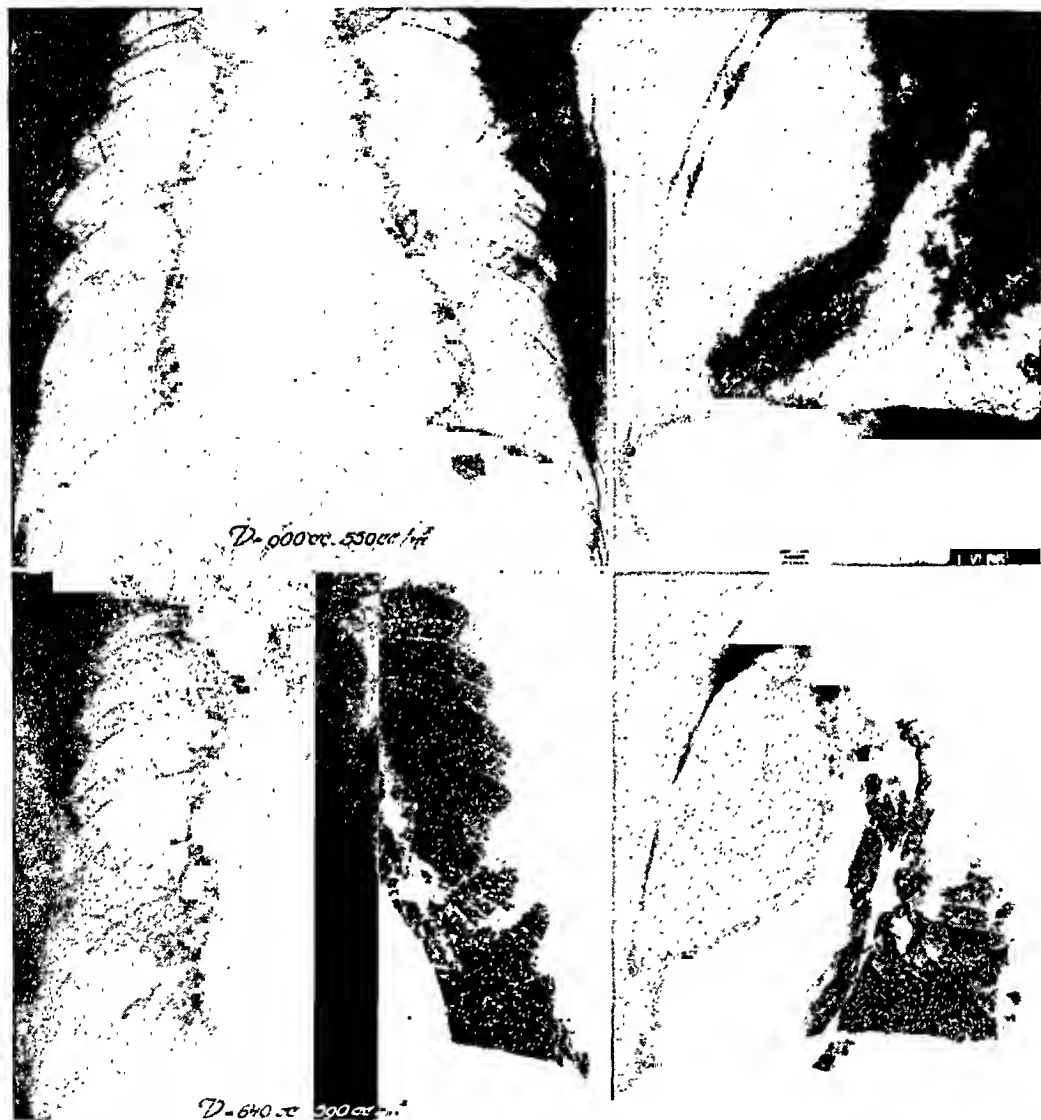


FIG. 4. The decrease in the size of the heart upon change from the horizontal position (upper films) to the standing position (lower films).

the upper and lower limbs falls as the patient is brought into an increasingly upright position. Taking into account the hydrostatic pressure in the lower limbs when the patient is vertical, it is seen that the fall in pressure is about the same in arms and legs. The diastolic pressure in the lower limbs is therefore about the same in both positions.

Pharmacological tests:

1. Adrenalin causes a pronounced increase both in blood pressure and acceleration of the pulse (figure 1).

POSTURAL HYPOTENSION

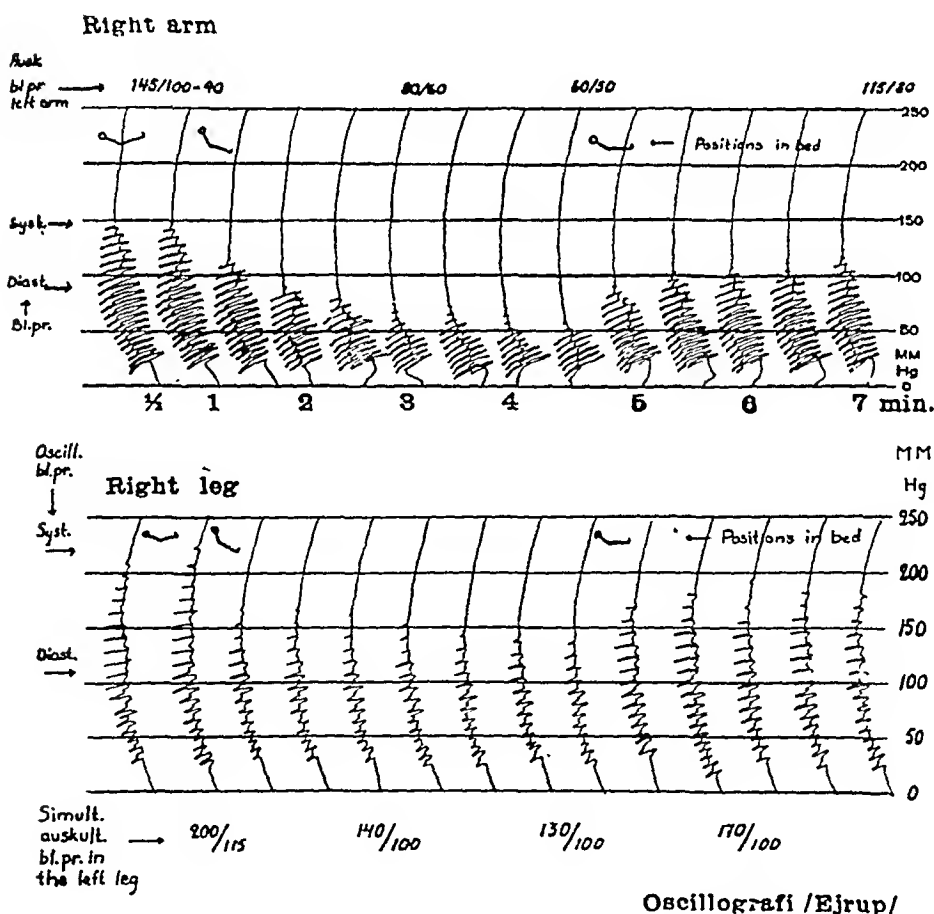
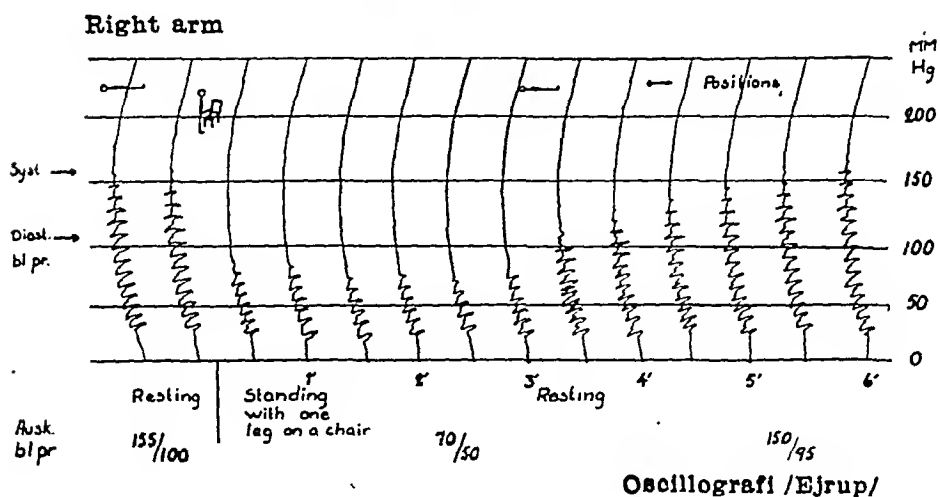


FIG. 5. Oscillography in different postures. *a* (above), November 9, 1944. *b* (below), October 11, 1945. Every vertical curve represents an oscillogram where the systolic pressure lies at the level above which we have no more oscillations. The diastolic pressure is marked by alterations in the form of the single pulsation of the oscillogram. Ejrup.¹⁵

2. Atropine does not affect the blood pressure.

3. Lobeline hydrochloride, injected intravenously with the patient recumbent: Injection of 3 mg. is followed 15 seconds later by a slight increase in depth of respiration. Injection of a further 3 mg. does not affect the respiration. Injection of a further 6 mg. causes three slightly deeper breaths.

4. Ephedrine. The patient took 1.25 to 2.5 cg. ephedrine every morning with such benefit that he was capable of light work.

The Circulatory Corpuscular Volume Determined with the Aid of Tagged Erythrocytes: Nylin^{40, 41, 42, 43} has shown in several investigations that labelled corpuscles injected intravenously into normal persons mix very quickly with those of the recipient, and that subsequently the specific activity of blood samples remains constant up to one hour after the injection. For this reason, it is possible to study any changes that may occur in the circulatory corpuscular volume within that time. This has been done on this case of postural hypotension on two different occasions. The first occasion was on November 17, 1944. Labelled corpuscles taken from the patient himself were injected intravenously while he remained in the standing position. Blood samples were then taken from the other arm at various intervals, and their activity determined with the Geiger counter. The patient's blood pressure in the erect posture was 75/50. Eight minutes after the injection he was allowed to lie down, and the blood pressure then rose to 210/110. Fresh blood samples were taken up to the eleventh minute after injection. The results are recorded in figure 6, which show that the specific activity falls during the first nine minutes. If, as is the usual practice, the circulatory corpuscular volume is calculated on the basis of the sample taken in the fourth to fifth minute the result is found to be 2065 gm., whereas if it is based on the ninth to tenth minute the result is 2380 gm. It might then be inferred that pooling of the blood in some reservoir occurs when the patient is in the erect posture, and that a corresponding dilution takes place in the horizontal position. This is probably incorrect, the true explanation being that the patient's low blood pressure in the erect posture results in a very slow circulation in certain parts of the body which delays the establishment of a state of equilibrium. In cases of postural hypotension, such equilibrium is not established before the end of the tenth minute.

The above explanation is also supported by a subsequent experiment (figure 6) which was carried out on June 14, 1945. On this occasion, the blood samples were taken much later, i.e. from the beginning of the tenth to the end of the thirty-fifth minutes. Figure 6 shows that the corpuscles were not evenly distributed until the twelfth minute when the head was raised to 28° above the horizontal and the blood pressure was only 60/45 mm. Hg. When the head of the bed was lowered to 25° below the horizontal, the blood pressure rose to 175/100 mm. Hg, and the specific activity remained constant from the twenty-second to the twenty-seventh minutes. In both positions, therefore, the calculated circulatory corpuscular volume was the same (figure 6). However, intravenous injection of adrenalin in the thirty-fifth minute caused a further rise in blood pressure to 215/115 (figure 6) and reduced the specific activity to an amount corresponding to a circulatory corpuscular volume of 1700 gm. (i.e. an increase of 130 gm.). This adrenalin action was unexpected, and has not been found to occur in normal cases.

The conclusion to be drawn from these studies on changes in the circulatory corpuscular volume in a typical case of postural hypotension, when the position of the body is changed, is that the very sharp fall in blood pressure is accompanied by a slowing of the circulation in various parts of the body and a consequent delay in the mixing of the corpuscles. Thus the calculated circulatory corpuscular volume will be too low if the blood samples

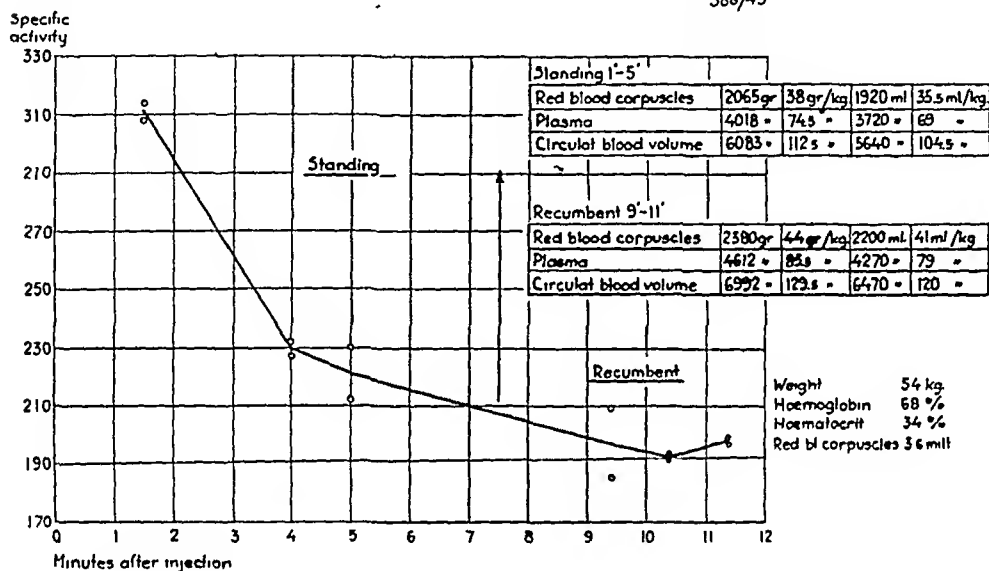
are taken too early. In cases of postural hypotension, the circulatory corpuscular volume is not reduced. Nylin has suggested that false conclusions have been drawn regarding the circulatory corpuscular volume in cases of shock and allied conditions because the blood samples have been taken too early. The essential problem in these conditions is the velocity of the circulation; since it is much lower than in normal subjects, the process of dilution takes much longer and equilibrium is reached much later.

Postural hypotension

Case 81

November 17 1944

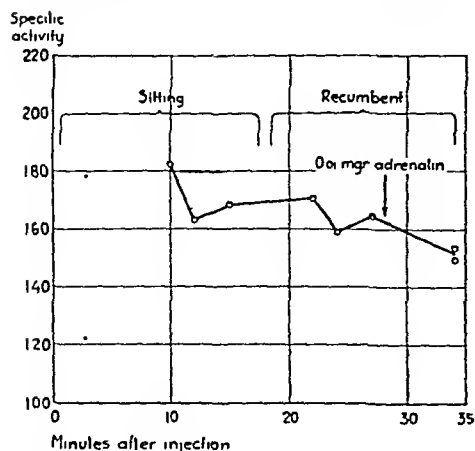
J. 929/44
386/45



June 14 1945

J 386/45

Weight 54 kg
Haemoglobin 68 %
Haematocrit 32 %
Red bl corpuscles 3.6 mill



Sitting 12-15'

Red blood corpuscles	1550 gr	29 gr/kg	1435 ml	27 ml/kg
Plasma	2970	55	2910	54
Circulat blood volume	4520	84	4345	81

Recumbent 22'-27'

Red blood corpuscles	1570 gr	29 gr/kg	1450 ml	27 ml/kg
Plasma	3140	58	3080	57
Circulat blood volume	4710	87	4530	84

After adrenalin 34'

Red blood corpuscles	1700 gr	31 gr/kg	1575 ml	29 ml/kg
Plasma	3410	63	3340	62
Circulat blood volume	5110	94.5	4915	91

FIG. 6. Circulatory corpuscular volume determined with aid of tagged erythrocytes.

OCCURRENCE

In the literature which is available to us, we have selected 33 cases in which postural hypotension appears to have been the principal complaint. We have eliminated a number of cases of tabes dorsalis, two cases of endocrine disorder, one case of syringomyelia, one case of hematomyelia and a number of cases of sympathectomy in which *asympathicotonic orthostatism* was one of the symptoms of the principal disease. In the 24 genuine cases, the ages varied between 34 and 72 years, 52 being the average. Eighteen were men and six women.

SUBJECTIVE SYMPTOMS

The most pronounced subjective symptoms are vertigo and exhaustion on standing, particularly in the mornings after meals and in the heat. Frequently the symptoms appear while walking and make manual labor impossible. They can lead to syncope, in which case the patient suffers so little discomfort that he sometimes does not know that he has fainted. This was the case with our patient, who fainted during one of the examinations; he displayed the above symptoms to a pronounced degree in other respects as well. Other usual symptoms are inability to sweat, impotence and reduced libido.

OBJECTIVE SYMPTOMS

When the patient is examined lying down, he appears to possess a perfectly normal circulation, and he often looks young for his age. The principal symptom is concerned with *blood pressure*. Even when the changes in position are small, raising the trunk causes a fall of systolic and diastolic blood pressures while lowering the trunk increases both. When the patient is lying down, lowering the head of the bed causes a rise (instead of the normal fall) in the systolic and diastolic pressures. The systolic pressure varies more than the diastolic and so the pulse pressure tends to follow the former.

The pulse is, in typical cases, amazingly constant, and this was true in our patient despite the violent changes of blood pressure. Electrocardiograms made in the resting state, immediately after light work, and in the erect posture respectively showed the frequencies in these three conditions to be 75, 79 and 75. Out of 22 cases of genuine hypotension reported in the literature, 11 had unvarying pulse, six abnormally small pulse variations and five larger variations. In cases of tabes dorsalis,⁵⁰ the pulse only underwent small variations, but they were considerable in cases occurring after sympathectomy.

Heart volume. The volume of the heart of our patient was found by roentgen-ray examination to be 900 c.c. (550 c.c./sq.m. body surface) lying down, and 640 c.c. (390 c.c./sq.m. body surface) standing.

The electrocardiogram did not display the abnormal P- and T- and diastolic waves which are seen when cases of *sympathicotonic orthostatism*

are examined in the erect posture. As a rule no abnormalities of note are seen on the electrocardiogram, and in our case it was negative even after a hypoxemia test and after work.

Renal function. Diuresis decreases in the erect posture even in persons with normal circulation.² It is natural that this should be more pronounced in orthostatic cases. Persons suffering from postural hypotension often excrete very little urine during the day, when they are up and about, but instead are afflicted with nocturia.^{7, 30} Similarly, water tests yield widely different results depending on whether the patient is lying down or is on his feet. In the former case, the excretion is large and the dilution normal, in the latter case the excretion is reduced and the specific gravity higher.^{12, 21, 44} We obtained corresponding results with our patient by merely lowering the foot of the bed or raising the head. The explanation is that the blood pressure is lower in the erect posture and as Corcoran et al.¹¹ found in one case, the renal circulation is reduced. Angiotonin relieved the hypotension and increased the circulation through the kidneys. After the patient had been kept in a head-up bed, sitting up caused only a temporary fall in blood pressure and the circulation through the kidneys was increased. Angiotonin at this stage reduced the renal circulation, which is the normal reaction. The slight increase in non-protein N which has been observed in a number of these cases, is probably connected with this defective circulation.

Blood. A more difficult problem is the moderate secondary anemia from which many of these patients suffer. In our case it was unusually resistant to therapy.

DIAGNOSIS

After *asymptathicotonic orthostatism*, with reduced systolic and diastolic blood pressures and, usually an unvarying pulse has been diagnosed, it remains to be decided whether it is one of the symptoms of endocrine disorder, nervous disease, etc., or whether it is itself the principal symptom of the postural hypotension described by Bradbury and Egglestone.

ETIOLOGY

Asymptathicotonic orthostatism is a symptom-complex, and consequently the etiology may vary. Various writers are, however, in agreement on one point—that the vegetative nervous system is injured. The pathological process may be luetic, as in the case of tabes dorsalis, or cystic, as in the case of syringomyelia. In the disease described by Egglestone and Bradbury, the orthostatic disorder is the principal complaint and its cause is not clear. As far as we know, only two cases of this type have been examined histologically post mortem, and in one of them the brain was not sectioned. The other case²³ displayed multiple encephalomalacia of the cerebrum and cerebellum, as well as endocarditis. In view of the patients' comparatively advanced age and the chronic nature of the disease, it is probable that the degenerative changes were in some cases arteriosclerotic in origin.

LOCATION

Impulses which release vasomotor reflexes for the regulation of the blood pressure can arise in the pressure-sensitive zones in the carotid sinus and aortic arch. The afferent impulses are conveyed in the glossopharyngeal nerve and the vagus (depressor nerve) respectively. In the ape, a sub-cortical center has been successfully demonstrated in the region of the hypothalamus, and a higher center in the frontal cortex which can stimulate the cervical sympathetic system and induce a rise in blood pressure and secretion of sweat.^{28, 29} It is believed that these centers also exist in man, as well as a vasomotor center in the medulla oblongata. The sympathetic and parasympathetic vasomotor impulses are closely coördinated, and a reduction of tone in one system is accompanied by a rise in the other. The parasympathetic efferent impulses travel in the vagus; the sympathetic impulses travel via the sympathetic chain to all the ramifications of this system. It is theoretically conceivable for a disturbance of vasomotor function to be located in part of the system, and we will now discuss the probability of its location in different parts.

The carotid sinuses and aortic arch constitute three separate areas so that only an extensive injury will abolish the reflexes by damage to the pressure-sensitive zones. A fall in systolic blood pressure in the erect posture, unchanged diastolic blood pressure and acceleration of the pulse occurred in two epileptics⁹ after bilateral denervation of the carotid sinuses and cervico-dorsal sympathectomy. This suggests *hyposympathicotonic orthostatism*, but the author has called it "pronounced postural hypotension." (Cervicodorsal sympathectomy did not by itself have these effects.)

It is possible to test the carotid body by stimulating it chemically with various pharmacological preparations,²⁵ and to test the carotid sinus mechanically by pressure from the surface. Ellis and Haynes¹⁶ administered sodium cyanide to a case of syringomyelia and to a diabetic with cryptogenic hypotension and obtained normal reactions in both cases. We could not detect any definite reaction in our own patient to repeated injections of lobeline hydrochloride. It is not permissible, however, to draw any conclusions regarding the carotid organs from this fact because it might be some other part of the reflex pathway that is injured. It thus seems unlikely, at least in pronounced *asymphathicotonic orthostatism*, that the cause of the disease is located in the pressure-sensitive organs.

The afferent pathways run in two different nerves and their interruption would therefore imply a rather unlikely multiple lesion.

Disturbances within the nervous system of such intensity and of such diffuse effect are often located in the cranial centers—in this case the vasomotor centers in the hypothalamus or medulla oblongata. If anhydrosis is also present, the most probable site of injury is the hypothalamus where the sweat center is also situated. This simultaneous disturbance of the vasomotor and sweat mechanisms, which are physiologically distinct and react

to different stimuli but are anatomically related, also suggests that the disturbance is organic rather than functional. The comparatively frequent occurrence of *asympathicotonic orthostatism* in *tabes dorsalis* can be explained by the location of the syphilitic degeneration, which occurs in the base of the brain in the region of the hypothalamus when Argyll-Robertson pupil is present.¹⁶ Parkinson's disease, which is the diagnosis in our case, is a disease located in the basal ganglia of the central nervous system, and it is unlikely that all the nervous symptoms have the same origin. There are probably at least two areas of origin and this is borne out by the fact that the symptoms first appeared at different times.

Location in the efferent pathways could produce the typical symptoms only if the lesions were very extensive.

To sum up, it is safe to say that in typical cases the pathological process is most probably situated in the region of the hypothalamus. In the only recorded case in which the central nervous system was sectioned, the pathological changes were multiple.

PATHOGENESIS

While there is general agreement that the essential features of the disease are mediated through the vegetative nervous system, there is much disagreement regarding its pathogenesis. Theoretically, the disturbance may follow an abnormal pooling of blood in the peripheral veins (i.e. group A in the table of regulatory mechanisms) or defective compensation by the sympathetic system (group B) or of course a combination of the two. There are two principal schools of thought:

MacLean, Allen and Magath consider that the disease is due to diminished venous return owing to increased pooling of the blood. They support the claim that diminished venous return is the cause by invoking, *inter alia*, the results obtained with Flack's test.¹⁸ In this test, the subject increases his intrathoracic pressure by blowing up a column of mercury, the time for which certain pressures can be maintained being measured. These patients are found to give up sooner than normal persons, when standing erect. These authors also point out that these cases display normal vascular reactions to changes of temperature. This temperature reaction is, however, the work of short pathways which do not reach the cranial centers and so it does not appear to eliminate the possibility of damage to the long reflex pathways.

Stead and Ebert belong to the other school. They have compared the volume of blood in the lower limbs of two patients lying and standing (at syncope) with that of healthy persons in corresponding positions and found them to be the same. They have also shown that in one of their patients, lying down, the reactive hyperemia after occlusion with an inflated cuff was sufficient to cause a severe fall in blood pressure, whereas in healthy persons the pressure falls only slightly. On the basis of these experiments, they formulate their view as follows: "Therefore, the primary cause of postural

hypotension is not the pooling of an abnormal amount of blood but presumably an abnormal response to the pooling of a normal quantity of blood." They consider the "abnormal response" to be defective vasoconstriction.

These two views may appear incompatible, but on close examination they are seen to be connected and even to constitute two sides of the same mechanism. MacLean et al. are doubtless right in stating that there is a diminished venous return, but they go astray when they attribute it to increased orthostatic pooling of the blood. This does not, at any rate, occur in every case, as Stead and Ebert have demonstrated and stressed. On the other hand, the defective vasoconstriction which the latter consider to be the essential factor probably gives rise, secondarily, to a diminished venous return. Constriction of the vessels is after all the basis of the normal, compensatory mobilization of blood from other regions which helps to maintain the return of blood in the erect posture. Moreover, owing to the absence of vasoconstriction, the arterial bed does not adapt itself to the diminished cardiac output. It is considered to be a sign of defective vasoconstriction if pallor does not manifest itself in syncope, and if the diastolic (in addition to the systolic) blood pressure falls (Stead and Ebert).

Another important factor is the absence of any acceleration of the pulse, which normally increases the cardiac output. Both vasoconstriction and acceleration of the pulse are, however, initiated by the same mechanism—a vasomotor, sympathetic reflex. It is possible that in some cases there may also be abnormal pooling of the blood due to defective vasoconstriction in the venous system. This, however, is not necessary for the appearance of the symptoms.

To sum up, one can say that in *asympathicotonic orthostatism* reflex regulation of the blood pressure and pulse rate is absent, probably owing to a lesion in the cranial centers.

COURSE

Recovery is reported in one or two cases. The majority of patients have not been observed for more than a few years, and during this time the only spontaneous variations in their condition are those that have accompanied changes in season and temperature.

PROGNOSIS

The prognosis must depend upon the disease ultimately responsible for the condition. The orthostatic complaint involves certain dangers owing to the patient's tendency to syncope, but since this occurs regularly and is preceded by a prodrome, the patient learns to avoid situations which give rise to it.

THERAPY

Causal therapy is conceivable in a few cases, such as *tabes dorsalis*. The chances of cure are, however, slight.

Symptomatic therapy may be based on two different principles: (a) One method is to reduce the orthostatic movement of the blood, making the organism less dependent upon the regulatory mechanism. The "water bath" experiments conducted by Stead and Ebert⁴⁹ show very well the effect of this treatment. Leg bandages and abdominal belts have also been tried, with varying success.

It is of course, difficult to make such therapy effective because it really needs to be applied both to the lower extremities and to the splanchnic area.

(b) The defective vasomotor reflex mechanism, which is incapable of fluctuating sympathetic activity, cannot be replaced by any pharmacological preparation. Sympathicomimetic substances will, however, raise the general level of the blood pressure and pulse rate and thus prevent the blood pressure and cardiac output from falling in the erect posture to the syncope level. As the reflex cannot be replaced, some fall of blood pressure is inevitable.

Ephedrine hydrochloride is the substance most commonly employed.^{1, 6, 7, 10, 11, 13, 16, 20, 27, 30, 31} Out of 15 recorded cases, the effect was said to be good in 12, but in two of these there were pronounced secondary effects—tremor and insomnia. In one case, the patient grew accustomed to the substance and its effect deteriorated, while in two cases it was of no use. In our case, results were obtained with a small morning dose. Paredrine and angiotonin have also been tried, as well as benzedrine, alone or in conjunction with ephedrine and paredrine as recommended.³¹ Ergotamine also raises the blood pressure but gives rise to anginous pains. The administration of medicine should be spread over the whole 24 hours, but should be most frequent in the morning and should begin with one dose before rising. It is worthy of note that the rise in blood pressure does not always give the patient corresponding subjective relief.

(c) Treatment with the head-up bed is, fundamentally of a different kind.^{11, 27, 35, 36} The patient sleeps in a bed of which the head end has been raised about 20° above the horizontal. This method makes use of the organism's power of adjustment either by stimulating the reflex mechanism or by transferring tissue fluid from one region to another. The fact that the effect is heightened by administration of plenty of liquid and salt suggests the latter alternative. MacLean et al.³⁶ claim to have demonstrated an increase in the circulatory blood volume and in the tissue fluid during this treatment. They report good results in the majority of cases, and immediate relapse on returning to a flat bed.

DISCUSSION

Pulse. The virtual constancy of the patient's pulse throughout a particular series of experiments but under different experimental conditions is striking. The frequency remained unchanged when the blood pressure varied between 180/125 and 75/60 as the patient's position was changed. Similarly, the pulse rate was not affected by hypoxemia tests, and an electro-

cardiogram showed that it was the same immediately after as it had been just before light work. It seems natural to suppose that the patient's poor capacity for manual work is connected with this unvarying pulse.

Blood pressure. In *asympathicotonic orthostatism*, there exists not only postural hypotension but also a certain degree of postural hypertension. The latter is of less practical importance, but it is of theoretical interest. In normal subjects, lowering the head of the bed causes an immediate initial rise in blood pressure which stimulates the vagus via the pressure-sensitive organs and so leads to a fall in pulse rate, dilatation of the vessels and consequent fall in pressure. This reaction is absent in *asympathicotonic orthostatism*. One can say that owing to the disease in the vegetative nervous system, the blood pressure is not regulated in accordance with the position of the body, i.e. that the disorder is a vegetative postural tension disorder.

The circulation through, for instance, the hand^{27, 48} appears to be less reduced by a given fall in blood pressure than in normal individuals. This explains why these patients remain conscious at blood pressures which in normal persons would lead to syncope.

PHARMACOLOGICAL PREPARATIONS

Adrenalin. The action of adrenalin on our patient, and in all the published cases, was normal, i.e. it caused a considerable acceleration of the pulse and rise in blood pressure.

Atropine, which normally accelerates the pulse and raises the blood pressure by inhibiting the action of the vagus, exerts no action in typical cases like ours. This, as Bradbury and Egglestone have already pointed out, is remarkable in view of the fact that the main feature of postural hypotension is the diminished reactivity of the sympathetic nervous system. As these writers have suggested, it is possible that the sympathetic system is in such a low state of tone that its action is not felt even when vagal tone is reduced. One might also, however, seek the explanation in close coördination that exists between the sympathetic and parasympathetic systems, and suggest that there may also be a disturbance of the parasympathetic vasomotor reflex mechanism. This hypothesis is supported by the following observations:

When the *asympathicotonic orthostatic* patient is raised, his organism does not react to the sympathetic stimulus provided by the fall in blood pressure, but neither does it react to the vagal stimulus provided by the rise in pressure which occurs when the head is lowered. Both circumstances are equally pathological, but only the former gives rise to symptoms. In *sympathicotonic orthostatism*, in which the vegetative nervous system reacts adequately, no abnormality should be observed on lowering the head.

Pilocarpine has been tried by a number of authors.^{1, 7, 54} Although the majority of these patients had declared themselves incapable, or scarcely capable of spontaneous sweating, pilocarpine has caused at least a partial secretion.

In cases where two factors of such fundamental importance to the circulation as blood pressure and pulse rate no longer react reflexly to different situations, the determination of the circulatory blood volume should provide important information. Unfortunately, very little is to be found on this subject in literatures. MacLean, Allen and Magath have attempted to determine the circulatory blood volume by means of the plasma method (congo red method). They found the volume to be reduced in the case in question, and observed that it increased as the patient's condition improved.

Our studies on the circulatory blood volume with the aid of labelled corpuscles indicate that in cases of postural hypotension the circulation in the erect posture (particularly in the lower part of the body) is much slower than in normal subjects. This suggests that the venous return from that part of the body must be reduced. The fall in the velocity of the circulation is probably a secondary effect of the severe damage to the reflex mechanism which regulates pulse rate and blood pressure.

Electrocardiogram. The changes seen in the electrocardiogram in cases of *sympathicotonic orthostatism* present an unsolved and interesting problem. In *asympathicotonic orthostatism*, no changes are observed despite the exceptionally low blood pressure and this also invites speculation. It perhaps supports the theory put forward by Ewert and Nordenfelt that the changes are normally due to an increase in sympathetic tone; when the sympathetic tone is very low, as it is in these cases, the electrocardiogram remains unchanged. But these observations can also be brought into line with the anoxemia theory (Åkesson). In postural hypotension, as in the Bezold reflex,²⁶ there is low blood pressure and a low pulse rate. But the Bezold effect is regarded by Jarish as a protective mechanism which can come into operation in the event of, for instance, infarct in the heart,¹⁴ improving the coronary and relieving the main circulation. It, therefore, appears conceivable that there is an adequate blood supply to the myocardium in *asympathicotonic orthostatic* cases even when syncope occurs, so that the latter need not modify the electrocardiogram even if anoxemia does so.

It is abundantly clear from the above that the reported case is a typical instance of *asympathicotonic orthostatism* as defined in this paper, i.e. a condition in which the organism is unable to regulate its pulse rate and blood pressure in different positions.

The probable cause of the condition is a pathological process (or processes) in the medullary reflex center for control of the blood pressure. The general clinical picture corresponds to a unilateral Parkinson disease which has probably been caused by similar lesions higher up in the brain stem. The presence of anhydrosis suggests that the lesions are located in the region of the hypothalamus.

SUMMARY

1. The literature relating to postural hypotension has been carefully reviewed.

2. A typical case of postural *asympathicotonic hypotension* has been examined from various angles.

3. The circulatory disorders occurring in these diseases have been the object of particularly comprehensive investigations.

4. The case in question was very sensitive to very small changes in position. In the recumbent position, the systolic blood pressure was 90 mm. Hg; sitting 64 mm.; standing 30 mm. (syncope).

5. The circulation is abnormally slow when the patient is in the erect posture. The even distribution of injected corpuscles therefore takes much longer than in normal cases. Blood samples taken too early from the veins give false results, i.e. the calculated circulatory blood volume is too small.

6. There was no change in the rate of the heart or in the electrocardiogram in different positions.

7. Neurological examination revealed a unilateral Parkinson's disease.

8. The fundamental factor in the disease appears to be the absence of reflex regulations of the blood pressure and pulse rate.

9. The pathological processes are probably located in the medulla oblongata and in the region of the hypothalamus.

10. We propose that typical cases of postural hypotension should be called *asympathicotonic hypotension*.

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PAIN MECHANISMS AND THE FRONTAL LOBES: A STUDY OF PREFRONTAL LOBOTOMY FOR INTRACTABLE PAIN*

By WALTER FREEMAN, M.D., Ph.D., F.A.C.P., and JAMES W. WATTS,
M.D., F.A.C.S., *Washington, D. C.*

PHILOSOPHERS may argue as to whether pain is a sensation or an emotion. As a sensation it has a threshold, a quality and a localization. Pathways for the transmission of pain run together with the pathways for temperature sensation within the central nervous system. Interruption of these pathways abolishes at least some aspects of pain, while other aspects may be even exaggerated.

On the other hand, pain is an emotion, vaguely to acutely uncomfortable, like fear, disgust and sadness or longing. It has a pervasive, insinuating, all-encompassing manner of concentrating the attention on the affected part and of arresting other mental activities. It produces alterations in the visceral mechanisms akin to those observed in fear, shock and rage. It is accompanied by an uncomfortable preoccupation with the future consequences of the pain. It seems likely that pain can be produced by emotional states pure and simple, and common experience has given rise to such terms as "a headache," "a pain in the neck," "it gripes me," "I got a misery," "heart-ache," "condolence," "sympathy."

The physician is called upon not infrequently to decide whether the pain complained of is explainable on the grounds of structural disorders that can be corrected by surgery, or on the grounds of functional disorders in which surgery can be positively detrimental. Some painful conditions are obviously in the surgical field such as fractures and wounds, strangulated hernia and acute appendicitis. Others are just as clearly in the medical field such as the headache after an alcoholic bout or the cramps of the menstrual period. There are many painful conditions of psychosomatic aspect that call for management of the patient in his relation to his environment. Discontent may reveal itself in any system or any organ with painful sensations that may be actually disabling. It is hardly necessary to belabor these facts, which are within the ken of every physician.

Some 10 years ago we had under observation a middle aged woman who obviously was suffering from an involutional depression with considerable agitation and a superimposed barbiturate intoxication. She tossed about in bed complaining bitterly of pain about the anus. Local examination revealed a number of hemorrhoidal tabs without any sign of recent inflammation. The lamentation was almost constant: "Oh, Doctor, please do some-

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From the Department of Neurology and Neurological Surgery, George Washington University.

thing for my hemorrhoids; I can't stand the pain, please give me some ice to put on them. This misery is terrible. I can't sleep, I can't eat, my bowels can't move, I feel so awful." Her attention could be distracted for a few moments by inquiring about her heart or her stomach or her knees, or her head, all of which, to judge from her statements, were continuously painful, but these received scant consideration when the rectal distress was mentioned.

The history indicated that she had been left a widow with two small children and had supported herself as a bookkeeper, looking after the house as well. She was described as a worrier, of nervous temperament, and inclined to cross her bridges before she came to them. The psychosis was preceded by a rather prolonged period of exhaustion during which the patient forced herself, got little rest, and finally collapsed, in what was described as a heart attack. The patient was sallow and flabby with cyanosis of the extremities, the blood pressure was 170 mm. Hg systolic and 90 mm. diastolic, there was a slight anemia and a non-functioning gall-bladder. One kidney had been removed some years previously. The patient was so obviously ill that renewed studies of the gastrointestinal tract were undertaken, but with negative results.

Prefrontal lobotomy was performed October 6, 1936 with spectacular results. The next day she extended her hand in smiling greeting, said she felt fine, was rather bewildered and did not know her head had been operated on. She vomited several times on succeeding days but was not in the least perturbed. She never mentioned her hemorrhoids. Convalescence was rapid and before the end of the month she was resuming her household duties. She returned to her work in December and kept it up for eight years before retirement. Then during the acute manpower shortage she returned to work for another year, finally retiring on her 70th birthday. She continues to live comfortably at home. She has practically no recollection of the six months' illness previous to operation. When questioned about hemorrhoids she denies that she has any. She has fattened up; the blood pressure has risen over a period of years to 210/110 but she has experienced no distress. Even though she is a poor sleeper she does not complain.

We were dealing in this case with a patient whose complaints were out of proportion to the anatomic deviations found. There can be no doubt that she was suffering, but the suffering could not be relieved by attention to the local conditions. The pain was the expression at the somatic level of a profound melancholia, and the prefrontal lobotomy was undertaken for the relief of the mental condition. When that was cleared up the somatic expression of the melancholia disappeared and was forgotten. It is easy in this case to pass it off as of no particular significance. That the pain disappeared was to be expected. But a deeper significance lies in the fact that it was pain in the beginning. It may be asked how melancholia can produce unbearable pain of such severity that the whole organism suffers, and without any discernible cause. In the present state of our knowledge we have to be content to call it psychalgia and let it go at that. We don't know.

A slightly different problem was presented two years ago by a middle aged woman who had had a pain in her back ever since she could remember, bad for 28 years, and especially bad for three years, keeping her in bed much of the time. In addition there were many other somatic complaints: "I guess it is what they call arthritis and neuritis. It wasn't bad until after the children came and that just ruined me." She went into prolonged and wandering detail about the doctors she had visited and their prescriptions. She admitted she was nervous and depressed, that she worried a lot and slept with one eye open and had crying spells. Her bones ached and her heart pounded, her face flushed and her voice gave out; she couldn't get her breath and she had a tightness in the throat. She was light-headed and had a roaring in her ears.

This patient weighed only 79 lbs., was thin to the point of emaciation, with a scaphoid abdomen through the walls of which most of the organs were palpable. The movements of the intestines were easily visible under this parchment-like membrane. Scars betokened removal of the appendix, uterus, gall-bladder. The monologue continued through the examination. In this case it was perhaps of significance that all the symptoms were induced or exaggerated by voluntary hyperventilation. They quieted down slowly and the patient could not voluntarily restrain herself from sighing at frequent intervals.

Prefrontal lobotomy was undertaken under local anesthesia on March 1, 1945. During the operation one of us placed his hand lightly upon the abdomen where a rounded firm mass, freely movable, probably represented the spasmodically contracted pylorus. The patient protested against this much more than she did against the surgical procedure on her head, begging the doctor to remove his hand, that it hurt so, that she couldn't stand it. With the severing of the final quadrant in the frontal lobes the patient stopped complaining and the mass disappeared.

Convalescence was rapid, the complaints disappeared, she resumed her housekeeping but was rather indolent and sarcastic. When her pains were mentioned she stated that she still had them, but "I don't bellyache any more; it don't get you nowhere." She has gained 40 lbs. and looks years younger, gets along on very little sleep and her energies and disposition are improving even after two years.

There is a clue in this case to the genesis of the pain. The patient was afflicted with an anxiety syndrome accompanied by hyperventilation. During periods of stress when the carbon dioxide was eliminated in excessive quantities there was evidently some increased tension of both smooth and striated musculature, which in a rather sensitive individual could definitely become painful. The lobotomy reduced the emotional tension and along with it the hyperventilation. Furthermore, it has been recognized as an important part of the lobotomy syndrome that preoccupation with the self is radically removed, and thus the individual is no longer able to pay attention to phenomena arising from the bodily organs. We may well call this individual a

hypochondriac and argue that she is exaggerating normal sensations beyond the limit, but in a case like this, of such duration and severity, there is little likelihood of relief by medicinal or psychotherapeutic aids. Pains associated with such emotional perturbations are practically beyond reach, even though they are not associated with any observable anatomic deviation.

The lightning pains of *tabes dorsalis* are not generally thought of as being of psychic nature, but these also subside after prefrontal lobotomy. For 10 years or more we followed a patient in the clinic who had been given malaria with satisfactory arrest of the disease. Yet the pains continued. As long as he was resting quietly at home they did not bother him much, but as soon as he resumed activity they became increasingly incapacitating. This man drove a taxi when he was able to secure morphine, but without the drug he was helpless. He made as high as \$100 per week during the war period, but had to spend \$80 for the injections several times a day. Finally deciding that it was not worth while he quit trying to make a living. The psychic element in the pains came out particularly in his statement: "I guess I could stand the pain if it wasn't for the thought of them coming on." The physical signs had changed not at all over the prolonged period of observation and treatment. When one of his fellow-sufferers committed suicide he accepted the idea of prefrontal lobotomy. This was carried out on December 4, 1944.

Following operation narcotics were discontinued and the patient gained 50 lbs. He ate and slept well, was indolent and outspoken and because of an uncongenial home situation he had to be confined in St. Elizabeth's Hospital where he promptly made himself useful. His perception of pain is as keen as ever, but he now speaks of the pains as twinges and can laugh them off. He goes about his activities without the threat of pain constantly hampering him.

Prefrontal lobotomy, as observed in many cases of mental disorder, abolishes concern with the future. It renders the patient rather obtuse in his social relationships, but much more so in regard to his relationship to his own body. The combination of these obtundities works positively toward the benefit of the individual who is faced with a chronic recurring painful condition. The patient can feel the pain but he isn't waiting for it to strike. Why the pain itself should disappear, should be described as a twinge when for a decade it had been described in almost anguished terms, still remains to be explained. Patients who have undergone lobotomy are often lively in their descriptions, but they miss deeper significances. Pain becomes an experience rather than an emotion, a fact rather than a threat.

About a year ago we operated upon a patient who had severe pain in the arm following the application of a caustic paste to a carcinoma of the right breast. The carcinoma had been present since 1939 and she spent most of her time from 1941 to 1946 in bed. Numerous injections into the brachial plexus and paravertebral regions resulted in an atrophic flail limb with moist, cyanosed, exquisitely painful causalgia of the whole arm from neck to finger-

tips. She whimpered when the arm was approached and cried out loudly when it was manipulated. Paravertebral novocain injection produced a slight alteration in the character of the pain but no significant relief.

Prefrontal lobotomy was carried out on May 15, 1946. Following operation narcotics were withheld and the patient had a severe reaction with convulsions, hyperthermia and delirium for several hours. During the following days she improved generally but still objected to any manipulation of the arm. It was noted on several occasions that the patient responded to examination by rapid and deep respiration, but in between times she talked rapidly and cheerfully, giggling frequently and entertaining her visitors with verbal sallies.

Q. Does your arm hurt?

A. Yes it hurts. I told Dr. Whatshisname and he said take it out of that bottle and pour it on the whatchamacallit.

Q. How about shaking hands?

A. No I can't give you that one. You can have the other all you want.

Q. What about this hand?

A. Oh; that's the hand you had ahold of.

Q. What about your hand?

A. What do you want to know about it?

Q. Does it hurt?

A. Does it hurt? Why of course it does (rather offhand).

Q. Does it bother you?

A. No, not so much. A little but not as much as it ought to.

Q. Why don't you use it?

A. I do use it all the time. (Shakes hands.) Well, how much is it?

The patient changed in the past year from a shrinking fear-ridden individual into a rather care-free somewhat boisterous person who was just as disabled as she was before operation, sitting all day in her chair until her husband guided her to bed. She grunted and overbreathed whenever the arm was moved and if anything the arm had become less sensitive to pinprick and vibration. The color was more nearly normal, there was no tremor or sweating and the atrophy had not progressed. She stated that the arm was constantly painful, but as soon as the arm was released she immediately changed the subject and talked garrulously about other matters.

There can be no doubt of the severity of the anatomic changes in the right upper limb. Nor can there be much doubt that it is sensitive and painful. But following prefrontal lobotomy the attitude of the patient toward the disabled arm underwent a profound alteration and she not only tolerated examination without flinching but made slight use of the arm, pulling it away with the left hand when it got in her way. Chiefly conspicuous, however, is her inability to concentrate her attention upon the limb. It has

become a mild nuisance instead of the dominant feature in her distressed existence. The arm no longer serves as a constant reminder that she faces a crippled and pain-ridden life, with death from cancer as the only relief. She is childishly euphoric and interested in external events rather than personal anguish. The pain remains but the reaction to pain is profoundly altered.

Among the painful conditions that defy the ingenuity of the physician, that associated with certain focal lesions of the brain is almost without equal. Softenings and hemorrhages in and about the thalamus give rise to a peculiar disagreeable gnawing and aching, burning and grinding pain which make the thalamic syndrome one of the most dreaded. Individual variation is considerable, in that some people bear their suffering with fortitude, while others are emotionally upset, sometimes to the point of psychosis. The pain is brought on by exposure, activity and emotional perturbation, from which there is little chance of complete escape except by remaining bedfast. Sedatives help more than analgesics, but the prolonged character of the malady, often extending over many years, renders drug treatment unsatisfactory, and physiotherapy is distressing.

We operated upon two patients with this syndrome in which the pain was altogether disabling and in addition was the cause of disruption of the household. One of the patients died shortly after operation so that no satisfactory observation could be made but the other patient has been greatly relieved and has returned to work as a typesetter. He suffered a mild stroke in 1944 with recovery in the course of a few weeks, but the painful phenomena were prolonged and severe. He was able to stand firm pressure over the upper limb much better than light stroking, and scratching the part was unendurable. He guarded the hand much as a patient with causalgia does. Yet objective examination showed only slight reduction in the acuity of sensation in the fingers, with some disturbance in the sense of position. Following prefrontal lobotomy the sensibility remained exactly as it was before the operation. He winced when his hand was scratched or when ice was applied, but he permitted these tests to be repeated. Before operation they aroused so much distress that one application was met with prolonged and reverberating pain.

Other observations have concerned painful stumps and phantom limb, atypical facial neuralgia, crippling arthritis with continual complaint of pain, mucous colitis of many years' duration with constant abdominal distress, anginoid syndromes accompanying emotional disorders, neuralgia following herpes zoster, causalgia rebellious to multiple operations including multiple cordotomies. We observed one patient, a year after prefrontal lobotomy, during delivery of a child. This patient chatted gaily between pains, but with the onset of each one she screwed up her face, held her breath, grew rigid and manifested every indication of actual pain. But when the uterine contraction ended she was again cheerful and talkative. She delivered without mishap and went home on the fourth day.

These observations have led us to the belief that the frontal lobes are important structures, not so much for the experiencing of pain as for the evaluating of the sensation, the estimation of its significance in terms of the self and of the future. So often a patient comes to the doctor complaining of a pain that is difficult to describe. The pain is a gripping, a tightness, a gnawing, a burning, a grinding, an aching or a pressure, or any number of other descriptive terms. It is particularly easy to spot one of the functional cases when the patient describes the sensation as being "worse than pain." Then it is pain compounded with resentment, frustration, hostility, guilt, fear, anger and other emotional reactions to the environment and to the self. It was the observation of the emotional component in a number of patients who evidently had organic disease but were reacting to it more than appeared to be justified that caused us to investigate the subject further. One of our first patients of this type was suffering from recurrent carcinoma of the bowel with metastasis to the sacral plexus. There can be no doubt that the pain was hideous, but the patient's statement was revealing. When he was receiving an injection of morphine, he said to the nurse: "When the effect of this morphine wears off you won't let me suffer, will you? You'll give me another hypo, won't you?" Here in a nutshell is the reaction of the patient to his discomfort, not of the moment, but looking toward the future. By means of the frontal lobes we are apparently able to project ourselves into the future and to estimate what is going to happen at a certain time if certain conditions are met. This man knew that in three hours he would again be uncomfortable and would require morphine. This was what he was thinking of rather than the relief he would experience in the next few minutes. Following prefrontal lobotomy he was able to get along without opiates although the disease progressed to its fatal termination in four months. When asked about his pain he maintained that it was the same as it had been before operation, but he was not concerned about it. His emotional reaction to the pain was altered in that pain became merely another experience rather than a continual horror. Furthermore the imminence of death was not disturbing to him. When asked if he knew he was going to die, he replied: "Sure, everybody has to die, don't they." He was matter-of-fact about it, neither euphoric nor depressed. One could not call him apathetic, because he responded appropriately to those about him. It was just that his concern with himself and his emotional attitude toward his disease and toward the consequences were accepted at face value rather than incorporated in a chain of horrendous circumstances.

The frontal lobes are apparently essential to foresight and to insight. These faculties are still present after prefrontal lobotomy, but the emotional charge that gives color to them, makes them come alive, and determines the behavior of the individual, apparently has its origin in the thalamus. Following prefrontal lobotomy the cortex remains practically unaltered, but the retrograde atrophy of the thalamus is notable. It may be that the atrophy of the thalamus permits the dying out of the emotional charge since not in-

frequently there is some persistence of the phenomena of pain and the reactions to pain just as there is persistence of the hallucinatory experiences for a time after prefrontal lobotomy in psychotic states. With the passage of time the phenomena show a rather orderly change. This could be observed most clearly in another tabetic patient who had been under drugs for nearly 20 years. At intervals before lobotomy he would react to a lightning pain by grabbing the part and rubbing it vigorously with an anguished expression on his face. Following operation he continued to have the pains and to react to them as before, but the haunting fear of them disappeared and thus changed his entire outlook on life. He would grab his knee and rub it vigorously, but when asked if it were painful he would deny it. This reaction continued for months after operation, the motor component outlasting the sensory, and the affective disappearing first.

Prefrontal lobotomy has a beneficent action upon pain whether it is primarily mental or primarily physical. It does not interfere with the perception of pain, but rather with the evaluation of pain. It does not relieve the pain, but rather the disabling reaction to pain, the fear of pain. It does so apparently by eliminating the emotional component arising from the thalamus.

While the indications for prefrontal lobotomy are not yet precise as far as painful conditions are concerned, in a general way we believe that it is valuable in those cases where pain of whatever origin is producing suffering and disability and in which the outlook for improvement under more conservative measures is unsatisfactory. The operation can be safely performed in the presence of serious visceral disease, since it is not a shocking procedure, and the relief is immediate and gratifying. We believe it should be employed more often in patients with severe pain.

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THE PROBLEM OF MALIGNANT HYPERTENSION AND ITS TREATMENT BY SPLANCHNIC RESECTION*

By MAX M. PEET, M.D., *Ann Arbor, Michigan*, and EMIL M. ISBERG, M.D.,
Assoc., *Miami Beach, Florida*

MUCH too frequently the clinician's interest in the problem of malignant hypertension has been one of diagnostic curiosity only. He has accepted both a hopeless prognosis and his personal inadequacy to cope with this dreadful disease. So he concerns himself with the problem of differential diagnosis, follows his patient to the autopsy room, and then takes pride in his capability for having differentiated this disease from terminal glomerulonephritis.

It is indeed important that the clinical entity of malignant hypertension be recognized. Diagnosis must be reached without temporization. However, once the diagnosis is made, arrangements for treatment by splanchnic resection should be completed, for timely surgical treatment offers a ray of hope to the victim of this terrible malady.

DIAGNOSIS

Each case in this study fulfilled the following diagnostic criteria for malignant hypertension: (1) a rapidly-progressive, deteriorating, clinical course of recent onset; (2) severe neuroretinitis with definite papilledema of 1 diopter or more (fundusoscopic examination of each patient was carried out in the ophthalmology department); (3) high diastolic blood pressure; and (4) evidences of constitutional involvement.

The extensiveness of the cardiac, cerebrovascular, and renal involvement in this constitutional disease will be demonstrated. The most significant objective sign is the retinal lesion. All patients in this series comply with the characteristics of Class 4 of the Keith-Wagener-Barker¹ classification.

THE SERIES

Number. One hundred and sixty-two cases were diagnosed as malignant hypertension and were surgically treated at the University Hospital between November 1933 and December 1941. Follow-up information was inadequate in 19 cases. This is a study of 143 patients, followed for five to 12 years since surgical treatment was performed.

Age. The youngest patient was 14 years, and the oldest was 57 years. Sixty-three per cent of the cases were 40 years and older (table 1).

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From the Section of Neurosurgery, University of Michigan Medical School and Hospital.

TABLE I

Age Distribution at Time of Operation

Age	Number	Per Cent
14 to 19	1	0.7
20 to 29	9	6.3
30 to 39	43	30.0
40 to 49	65	45.5
50 to 57	25	17.5

Sex. There were 88 males (62 per cent of the series) and 55 females (table 2).

TABLE II

Sex Distribution and Subsequent Deaths According to Sex

	Cases	Per Cent of Total Cases	Per Cent of Total Deaths
Males	88	62	65
Females	55	38	35

Duration of Hypertension. In 31 cases elevated blood pressure was discovered only after the sudden appearance of the severe manifestations of the disease; these may be considered "de novo" cases. All 31 presented themselves within one year of onset.

In the remaining 112 cases, the existence of hypertension was known prior to the time the disease started on its malignant course. There were 18 cases who had been known to be hypertensives for 10 to 17 years. In these 112 cases, malignant hypertension may be considered as an end stage of arterial hypertension.

Blood Pressure Distribution. The blood pressure ranged from 310 mm. Hg systolic and 190 mm. diastolic down to 190/116. Seventy-six per cent had diastolic levels of 140 mm. or higher; 31 per cent had diastolic levels above 155 mm.

TABLE III

Symptoms

Preoperative Symptom	Cases	Deaths	Cases Living 5 to 12 Years Postoperative		
			Complete Relief	Improved	No Change
Headache	128	106	10	10	1
Visual disturbances	98	84		13	1
Dyspnea	65	58	1	6	1
Dizziness	39	29	3	6	1
Fatigue	37	31		6	
Nocturia	32	30		1	1
Nervousness	31	25		5	1
Cerebral accident	29	23	6		
Weakness	25	23		2	
Epistaxis	15	12	3		
Angina	11	11			
Loss of weight	8	8			
Muscle pains	6	6			
Hematuria	5	4	1		
Convulsions	4	3	1		
Uterine bleeding	2	2			

SYMPTOMS

Headache was the most common complaint, and it was present in 90 per cent of the series (table 3). Visual disturbances occurred in 62 per cent and dyspnea in 45 per cent. Dizziness, fatigue, nocturia, nervousness, and the residuals of a cerebral accident were complaints in one-fourth of the patients. Weakness, epistaxes, angina, and loss of weight were less common. Muscle pains, hematuria, convulsions and uterine bleeding occurred in occasional cases.

CARDIAC STATUS

An electrocardiogram and teleroentgenogram were obtained preoperatively in 121 patients. The electrocardiogram was abnormal in 110; and definite cardiac enlargement was present in 103. Confirmed organic heart disease occurred in 91 per cent of the series.

The Electrocardiogram. Both definite left axis deviation and abnormal T-waves were present in 40 per cent of the preoperative tracings. Inverted T-waves in both Leads I and II were found in 28 per cent of the curves. Table 4 lists the incidence of each electrocardiographic abnormality, with the accompanying death rate.

TABLE IV
The Electrocardiogram in Malignant Hypertension

Preoperative Status	Cases	Deaths	Patients Living 5 to 12 Years Postoperative				
			Cases	Significant Improvement in EKG	No Significant Change	Worse	No Follow-up. EKG
A. Normal EKG	11	2	9		4		5
B. Abnormal EKG	110	98	12	2	2	2	6
1. Inverted T ₁	7	6	1	1			
2. Inverted T ₁ and T ₂	34	32	2	1			1
3. Inverted T ₂ and T ₃	3	3					
4. Definite L.A.D.	14	11	3			1	2
5. Both inverted T-waves and definite L.A.D.	49	43	6		2	1	3
6. Bundle branch block	2	2					
7. Evidences of previous myocardial infarction	1	1					

Heart Size. The prediction tables of P. C. Hodges and Eyster² for frontal area, and the tables of F. J. Hodges and Eyster³ for transverse diameter were used in determination of heart size from teleroentgenograms. A heart was deemed slightly enlarged when the variation was 11 per cent to 20 per cent greater than predicted normal for area or transverse diameter; moderate enlargement consisted of a variation of 21 per cent to 50 per cent greater than predicted normal; and marked cardiac enlargement consisted of a variation greater than 50 per cent above predicted normal.

Only 14 per cent of the patients had hearts of normal size. In 17 per cent

there was slight cardiac enlargement; in 48 per cent there was moderate cardiac enlargement; and in 21 per cent cardiac enlargement was marked (table 5).

TABLE V
Heart Size in Malignant Hypertension

Preoperative Status	Cases	Deaths	Patients Living 5 to 12 Years Postoperative				
			Cases	Significant Decrease in Heart Size	No Change	Increase in Heart Size	To Follow-up Tele-roentgenograms
Normal heart size	18	6	12		4	1	7
Slight cardiac enlargement	21	14	7	3			4
Moderate cardiac enlargement	56	54	2	2			
Marked cardiac enlargement	26	26					

KIDNEY FUNCTION

Preoperative studies of kidney function included the determinations of blood nonprotein nitrogen, urea clearance, maximum concentrating ability, and routine urinalyses. Excretory pyelograms were done in a majority of the cases. Tests of kidney function were completed in 138 patients prior to operation (table 6). Prior to September 1939 the concentration test was carried out over a period of 38 hours⁴; since then an 18-hour test⁵ has been used.

TABLE VI
Kidney Function in Malignant Hypertension

Preoperative Status	Cases	Deaths	Patients Living 5 to 12 Years Postoperative				
			Cases	Significant Improvement	No Change	Worse	No Follow-up Tests
Normal function	23	14	9	—	4	1	4
Impaired function	115	103	12	2	3	1	6
a. Slight impairment	55	44	11	2	2	1	6
b. Moderate impairment	47	46	1		1		
c. Marked impairment	13	13	0				

Normal kidney function was found in only 23 patients, or 16 per cent of the series. Forty per cent of the patients had slight impairment of renal function, with urea clearance values of 50 per cent to 65 per cent; and a maximum specific gravity of 1.020 to 1.023 on an 18-hour concentration test or of 1.022 to 1.026 on a 38-hour concentration test. Thirty-four per cent of the malignant hypertensives had moderate impairment of renal function, with urea clearance values of 20 per cent to 49 per cent and a maximum spe-

cific gravity of 1.013 to 1.019 on an 18-hour concentration test or of 1.015 to 1.021 on a 38-hour test.

Kidney function was markedly impaired in 10 per cent of the series. These cases each had a fixed specific gravity, urea clearance values of less than 20 per cent of normal, and elevated blood nonprotein nitrogen levels greater than 40 mg. per cent. None of these cases with azotemia were living two years after the operation.

CEREBROVASCULAR DISEASE

Twenty-nine malignant hypertensives, or 20 per cent of the series, had sustained one or more definite cerebrovascular accidents prior to operation.

COMPARISON OF CONSTITUTIONAL INVOLVEMENT

The marked prevalence of constitutional involvement in this group of hypertensives who each had severe neuroretinitis and papilledema is apparent from comparison with a group of hypertensives without papilledema. In a Peet and Isberg⁶ series reported previously, there were 325 hypertensive patients without papilledema; 58 per cent of these had cardiac disease, 15 per cent had cerebrovascular disease, and 12 per cent had impaired renal function. In the present study of malignant hypertension, 91 per cent of the patients had organic heart disease and 84 per cent had impairment of renal function.

SURGICAL TREATMENT

The operative procedure consists of bilateral resection of the greater, lesser, and least splanchnic nerves, and excision of the eighth, ninth, tenth, eleventh, and twelfth thoracic sympathetic ganglia. In the early operations, in addition to the splanchnic nerves, only the lower three dorsal ganglia were removed. The anatomical dissection is carried out entirely above the diaphragm.

This technic of splanchnic resection is performed bilaterally in one stage. The average operation time is about one hour. The postoperative stay in the hospital averages 10 to 14 days.

The operative mortality for patients with malignant hypertension is 10 per cent. Sixteen deaths occurred within 14 postoperative days in the 162 cases operated upon. For hypertensive patients without papilledema, the operative mortality is 1.6 per cent.⁷

TABLE VII

Survival of 143 Malignant Hypertensives at Intervals After Operation

Postoperative Time	Survivors
2 weeks	90%
6 months	71%
1 year	54%
2 years	40%
3 years	30%
4 years	26%
5 years	21.6%

TABLE VIII. Preoperative Data on 31 Cases of Malignant

Case	Sex	Age	Date of Operation	Known Duration of Hypertension	Symptoms
1. H. H.	F	44	6-2-34	3 years	Paroxysm. noct. dyspnea and exertional dyspnea, headache, cough.
2. W. L.	M	29	11-17-33	8 months	Headache, convulsions, fatigue, nocturia, rapid loss of vision.
3. C. L.	M	33	3-3-34	9 months	Convulsions, severe headache, vomiting.
4. H. W.	M	51	1-11-35	7 years	Visual disturbances, weakness, severe headache recent in onset.
5. A. H.	F	34	3-22-35	1 year	Diminishing vision, headache, insomnia, nocturia, dyspnea, palpitation.
6. I. S.	M	34	12-11-35	16 months	Complete incapacitation by headaches, weakness, fatigability, acute pulmonary edema.
7. E. F.	M	44	1-18-36	less than 1 year	Headaches, nocturia, paroxysm. noct. dysp. and exertional dyspnea.
8. P. S.	F	39	10-14-40	6 years	Blurred vision, headaches, dizziness, swollen ankles, exaggerated recently.
9. E. K.	F	34	3-6-37	3 years	Severe headaches, mental confusion, vertigo, dyspnea, palpitation.
10. M. C.	F	55	4-17-37	4 years	Severe headaches, epistaxis recently.
11. O. T.	M	35	5-8-37	8 years	Recent severe headaches, visual change, hematuria, dyspnea.
12. G. D.	F	37	6-18-37	2 years	Complete incapacitation from recent headaches, mental confusion, diminished
13. A. A.	M	48	6-19-37	3 years	Recent onset of blurred vision and headache, parox. noct. dyspnea, exertional dysp.
14. F. S.	F	46	12-11-37	15 years	Recent severe headache and blurred vision, dyspnea.
15. F. C.	F	48	1-6-38	17 years	Headache, insomnia, nocturia, recently markedly aggravated, dyspnea.
16. G. D.	F	27	2-4-38	3 years	Severe headaches, nausea, vomiting, dyspnea.
17. E. P.	F	42	3-24-38	4 years	Severe cardiac, headache, fatigue, dyspnea, angina.
18. V. H.	F	49	4-29-38	8 months	Severe headache, vertigo, nausea and vomiting, blurred vision, dyspnea, palpitation.
19. B. D.	F	34	1-26-39	12 years	Recent severe headache, tinnitus, epistaxes, diminished vision, parox. noct. dyspnea.
20. L. F.	M	52	2-24-39	10 months	Dyspnea, palpitation, severe headache, fatigue, vertigo.
21. P. L.	F	41	9-25-39	3 years	Severe headache, dizziness, fatigue, dyspnea.
22. R. B.	F	43	12-22-39	12 years	Severe headache of recent onset, fatigue, dyspnea.
23. E. K.	F	37	8-29-39	13 years	Severe headache, vertigo, weakness, visual disturbance, recent in onset.
24. L. D.	M	57	9-23-39	10 years	Severe blurred vision, epistaxes, vertigo, headache recent in onset.
25. M. J.	F	50	2-21-40	17 years	Recent severe headache, epistaxis, tinnitus, blurred vision, dyspnea
26. M. R.	F	44	3-4-40	9 months	Headache, diminished vision, fatigue, nocturia, dyspnea.
27. H. B.	M	36	11-15-40	1 year	Severe headaches, muscle pains, blurred vision.
28. N. H.	M	45	12-9-40	6 years	Severe headache, nausea, fatigue, blurred vision, nervousness.
29. L. S.	M	46	12-23-40	4 years	Recent onset of severe headache and blurred vision.
30. S. T.	F	45	4-3-41	4 years	Headaches, vertigo, blurred vision, nausea and vomiting, dyspnea.
31. E. S.	F	33	5-28-41	10 months	Headaches, fatigue, weakness.

Hypertension Having a 5-year Survival after Splanchnic Resection

Pre-op. B.P.	Cerebrovascular Disease	Cardiac Status	
		Electrocardiogram	Teleroentgenogram
240/165	—	Definite left axis deviation and inverted T in I and II	Slight cardiac enlargement +17% +10%
240/166	—	—	—
268/176	—	Definite left axis deviation with normal T-waves	Slight cardiac enlargement +10% +20%
245/140	—	—	—
235/165	—	Not definitely abnormal	No cardiac enlargement -22% -14%
215/139	—	Moderate LAD with inverted T in all leads	—
234/140	—	Definite left axis deviation	Moderate cardiac enlarge. +27% +10%
240/150	—	Definite LAD with abnormal T in I and II	Moderate cardiac enlarge. +45% +30%
296/140	* Left hemiplegia 5 months pre-op.	Inverted T in I and II	Moderate cardiac enlarge. +21% +19%
254/140	Left hemiparesis 6 months pre-op.	—	—
212/148	—	—	—
260/132	* Left hemiplegia 6 months pre-op.	Inverted T in I and II	Slight cardiac enlarge. +14% +10%
226/137	—	Right bundle branch block. Flat T in I; no T in II and III	—
240/140	—	Inverted T in Lead I. Prolonged Q-T interval	Slight cardiac enlarge. +19% +5%
238/118	—	Definite LAD with inverted T in I and II	No cardiac enlargement -14% -2%
212/134	—	Not definitely abnormal	Slight cardiac enlarge. +16% +10%
220/140	—	Moderate LAD with inverted T in I	No cardiac enlargement +9% +5%
280/140	—	Within normal limits	Slight cardiac enlarge. +14% +1%
200/120	—	Inverted T in I and II	Moderate cardiac enlarge. +38% +17%
204/126	—	Not definitely abnormal	Moderate cardiac enlarge. +24% +10%
280/140	* Left hemiparesis one month pre-op.	Inverted T in all leads. Slight left axis deviation	—
250/150	—	Definite LAD, inverted T in I	No cardiac enlargement +4% -2%
238/138	* Right hemiplegia 2 months pre-op.	Not definitely abnormal	No cardiac enlargement -6% +1%
218/116	—	Not definitely abnormal	No cardiac enlargement +9% +8%
270/160	—	Definite LAD suggesting LVE	Slight cardiac enlarge. +16% +18%
234/122	Rt. facial hemiparesis 6 mo. pre-op.	Definite LAD with inverted T in I	No cardiac enlargement 0 -1%
218/128	* Right hemiplegia 2 weeks pre-op.	Not definitely abnormal	No cardiac enlargement -9% +5%
204/134	—	Not definitely abnormal	Slight cardiac enlarge. +16% +11%
205/120	Left facial hemiparesis 2 mo. pre-op.	Not definitely abnormal	No cardiac enlargement +7% -2%
245/150	—	Definite LAD suggesting LVE	Moderate cardiac enlarge. +31% +20%
275/170	—	Moderate LAD. Inverted T in II and III	Moderate cardiac enlarge. +50% +26%

TABLE VIII. Preoperative Data on 31 Cases of Malignant Hypertension Having a 5-year Survival after Splanchnic Resection—*Continued*

Case	Kidney Status				Eyegrounds				
	Proteinuria	NPN	Maximum Concentration	Urea Clearance	K-W-B Grading	Papilledema	Hemorrhage	Exudate	Angiospasm
1. H. H.	++	33.3	1.024 ^L	—	IV	2 d	+	+	+
2. W. L.	+	30.3	1.014 ^L	105	IV	3 d	+	+	+
3. C. L.	+	27	1.021 ^L	95	IV	2 d	+	+	+
4. H. W.	++	—	1.025 ^L	59	IV	1 d	+	+	+
5. A. H.	+	33.3	1.022 ^L	53	IV	1 d	+	0	+
6. I. S.	+	—	—	81	IV	1 d	+	+	+
7. E. F.	+	—	1.029 ^L	81	IV	2 d	+	0	+
8. P. S.	++	35	—	42	IV	2 d	+	+	+
9. E. K.	++	35	1.027 ^L	108	IV	1 d	+	+	+
10. M. C.	+	27	1.025 ^L	88	IV	2 d	+	+	+
11. O. T.	+++	32	1.014 ^L	51	IV	1½ d	+	0	+
12. G. D.	+++	37	1.025 ^L	70	IV	1 d	+	+	+
13. A. A.	+	39	1.021 ^L	100	IV	2 d	+	+	+
14. F. S.	0	26	1.020 ^L	—	IV	2 d	+	+	+
15. F. C.	+	24	1.025 ^L	79	IV	1 d	+	0	+
16. G. D.	+	22	1.028 ^L	89	IV	1 d	+	+	+
17. E. P.	0	29	1.026 ^L	94	IV	1 d	0	0	+
18. V. H.	0	22	1.025 ^L	94	IV	1 d	+	+	+
19. B. D.	+	26	1.026 ^L	111	IV	2 d	+	+	+
20. L. F.	0	37	1.027 ^L	76	IV	2 d	+	+	+
21. P. L.	0	31	1.027 ^L	70	IV	1 d	+	+	+
22. R. B.	++	40	—	52	IV	1½ d	+	+	+
23. E. K.	++	40	1.021 ^L	50	IV	1 d	+	0	+
24. L. D.	+	39	1.024 ^S	75	IV	2 d	+	+	+
25. M. J.	+	29.2	1.019 ^S	78	IV	3 d	+	+	+
26. M. R.	0	37.8	1.020 ^S	123	IV	2 d	+	+	+
27. H. B.	++	32	1.021 ^S	130	IV	2 d	+	+	+
28. N. H.	0	25	1.031 ^S	—	IV	2 d	+	+	+
29. L. S.	0	30	1.036 ^S	128	IV	2½ d	0	0	+
30. S. T.	+	31.4	—	96	IV	1½ d	+	0	+
31. E. S.	+	31.1	1.022	55	IV	1 d	+	+	+

L = the long, or 38-hour concentration test; 1.029 is lower limit of normal.

S = the short, or 18-hour concentration test; 1.025 is lower limit of normal.

d = diopter.

RESULTS

Survival. Thirty-one patients of 143 with malignant hypertension survived five years after operation. This constitutes a five-year survival rate of 21.6 per cent (table 7). The preoperative data in each of these 31 cases are given in table 8.

Twenty-three cases were still living five to 12 years after operation; the five-to-12-year survival rate is 17 per cent. Eight patients died subsequent to living five postoperative years; five died during their sixth postoperative year, and one each died during the seventh, eighth, and tenth years.

Sixty-five per cent of the deaths were males; 62 per cent of the cases in the series were males.

Eyegrounds. In ten of the 23 living patients a recent fundusoscopic examination was recorded. In all 10 the papilledema had disappeared.

Blood Pressure. Recent blood pressure determinations were obtained in 21 living patients, five years and more after splanchnic resection. Four patients were maintaining blood pressure levels within normal range, below 140 mm. systolic and 90 mm. diastolic. In seven patients blood pressure was markedly reduced by 80 mm. or more systolic and 25 mm. or more diastolic, from the preoperative levels. In six cases there was significant reduction of 40 mm. or more systolic and 15 mm. or more diastolic. There was no significant change or an increase in blood pressure in five cases (table 9).

TABLE IX

Blood Pressure in 21 Living Cases, According to Postoperative Year

	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.
Reduced to normal 140/90 or less	1 L. W.	1 L. F.			1 F. S.		1 H. W.	
Marked reduction 80 mm. sys. 15 mm. diast. or more	2 P. S. E. S.	2 R. H. H. B.		2 E. K. M. C.				
Significant reduction 40 mm. sys. 15 mm. diast. or more	1 S. T.	2 E. K. L. D.	1 G. D.	1 O. T.				1 C. L.
No change or increased	2 M. J. M. R.	1 P. L.	2 F. C. E. P.					

Symptoms. Of 20 living patients who had preoperative headaches, 10 have enjoyed complete relief for five years and more, nine have been improved, and only one patient has experienced no change.

All except one of the 14 living patients who had preoperative visual disturbances have noted improved vision since operation. Of the three living patients who had epistaxes prior to operation, none have had any recurrence.

Of the 25 patients who complained of weakness, only two have survived five years and more. Only one of the four patients with convulsions was still living.

All 11 patients who complained of anginal seizures, all eight patients who noted weight loss, and all six patients who had muscle pains, have not survived five years since operation.

One of the five patients with hematuria was still living; both cases of uterine bleeding have died.

Cardiac Status. Ninety-one per cent of the series had organic heart disease prior to operation, and 12 of these patients are still living five to 12 years later. The other 11 living patients did not have heart disease prior to operation, and only one of them is known to have developed heart disease during the long post-operative period.

Thirteen patients with malignant hypertension manifested no evidences of cardiac involvement prior to operation, and 11 of them were still living five to 12 years later. It appears that if splanchnic resection can be performed early, before heart disease has occurred, the outlook can indeed be encouraging.

The Electrocardiogram. Of the 12 persons who had abnormal tracings before operation and who survived five to 12 years, recent curves were obtained in six. Two showed significant improvement. In one case the inverted T-waves in Leads I and II had returned to an upright position, and in the other the previously inverted T-waves in Lead I had reverted to normal. In the first case blood pressure has been maintained within normal range for six years since operation; in the second case diastolic pressure has been reduced 25 mm.

Heart Size. Five patients with preoperative cardiac enlargement had recent teleroentgenograms, and in all five, significant decrease in heart size had taken place. In one of these cases blood pressure was reduced to within normal range, and in each of the remaining four, significant reductions of 15 mm. and more of diastolic pressure had occurred.

None of the 26 patients with marked cardiac enlargement—variation greater than 50 per cent above predicted normal—survived two years.

Congestive Heart Failure. There were 16 malignant hypertensives who were in congestive heart failure and who were digitalized preparatory to splanchnicectomy. None of these patients were living at the time this study was made, but two survived five postoperative years, and both died during their sixth postoperative year. None of the remaining 14 were living three years after operation.

Although the outlook is indeed poor, the malignant hypertensive who is in congestive failure and who responds to digitalization need not be denied splanchnicectomy.

Kidney Function. Of 115 cases with preoperative impairment of renal function, 12 have survived five years or more. Eleven of these cases had slight impairment; only one of the 47 cases with moderately impaired function was living five years after operation.

None of the 13 cases with marked impairment of kidney function and azotemia survived two years.

Cerebral Accidents. Six patients who had sustained cerebral accidents prior to splanchnicectomy were still living and had suffered no recurrence. The malignant hypertensive with cerebrovascular disease stands just as good

a chance for five year survival after splanchnic resection as the malignant hypertensive without cerebrovascular disease.

The remaining 17 patients still living five to 12 years after operation had no cerebral accidents before surgical treatment and have had none since.

DISCUSSION

The study of 143 cases of malignant hypertension treated by splanchnic resection five to 13 years ago has revealed the following:

1. Malignant hypertension occurs more frequently after 40 years of age.
2. Sixty-two per cent of the series were males, and 65 per cent of the deaths were among males.
3. Twenty-one per cent of the cases may be considered "de novo"; in the remaining cases the existence of hypertension was known prior to the time the disease started on its malignant course.
4. The blood pressure levels were high; 76 per cent had diastolic levels of 140 mm. to 190 mm.
5. Headache, visual disturbance, and dyspnea were the most common complaints.
6. Constitutional involvement is extensive in malignant hypertension. Ninety-one per cent of the series had definite organic heart disease, 84 per cent had impaired kidney function, and 20 per cent had experienced cerebrovascular accidents.
7. The operative mortality in malignant hypertension is 10 per cent.
8. The five-year survival rate in 143 cases of malignant hypertension treated by splanchnic resection is 21.6 per cent.
9. All living patients receiving a fundusoscopic examination five years and more after operation showed no evidence of papilledema.
10. Four patients were maintaining blood pressure levels within normal range five to 11 years after operation. In 76 per cent of the living patients, blood pressure was either reduced to normal or significantly reduced, five to 12 years postoperative.
11. If splanchnic resection can be performed early, before heart disease has occurred, the outlook is good, for 11 out of 13 such cases of malignant hypertension were living five to 12 years after operation.
12. Improvement in the electrocardiogram and decrease in heart size are possible in those cases who survive five years and more.
13. Once kidney function becomes moderately or markedly impaired, splanchnic resection is futile. No case with azotemia survived two years.
14. Splanchnic resection is useless in those cases of malignant hypertension with marked cardiac enlargement—variation greater than 50 per cent above predicted normal.
15. The diagnosis of malignant hypertension was made only in those cases meeting our diagnostic criteria.

The few reports in the literature on malignant hypertension are indeed

ominous, and justifiably so. This disease is more rapidly fatal than many forms of cancer; untreated, it is as certainly fatal as untreated cancer.

Keith, Wagener, and Barker¹ have presented a series of hypertensive patients treated only with general measures and sedatives, and they have proffered this group as a good control for any specific form of therapy. Fair comparisons can be made between the present series and the 146 cases of malignant hypertension in the Keith-Wagener-Barker series, for the same criteria were used in making the diagnosis of malignant hypertension.

In the Keith-Wagener-Barker control series only 21 per cent of the patients with malignant hypertension were living at the end of the first year, 12 per cent were living at the end of the second year, 6 per cent at the end of the third year, 2 per cent at the end of the fourth year, and 1 per cent at the end of the fifth year. Only one patient with malignant hypertension in the control series survived five years.

Page⁸ studied 30 patients from the date of diagnosis to seven years later. At the end of that time five were still living, and three of these had been surgically treated by anterior spinal nerve root section. Of 21 cases medically treated, two survived seven years.

In the special study of Taylor, Kohlstaedt, Richter, and Page⁹ in which they clarify the differential diagnosis of malignant hypertension and terminal glomerulonephritis, all 10 patients with malignant hypertension died in four to 12 weeks.

Flaxman¹⁰ found that nine (34 per cent) of 26 cases of malignant hypertension with the diagnosis substantiated at autopsy in each, survived five years. His criteria for the clinical diagnosis and autopsy diagnosis of malignant hypertension were not given.

The five-year survival rate of 21.6 per cent obtained with splanchnic resection offers some hope to the malignant hypertensive, who otherwise is usually destined for early death.

Once the diagnosis of malignant hypertension is established, arrangements should be made for surgical treatment. Deterioration of the patient is rapidly progressive from week to week. The earlier splanchnic resection is carried out, the more can be salvaged.

Patients with malignant hypertension are poor surgical risks; the operative mortality is high. But in a disease so deadly, it is probably worth the 10 per cent operative risk for a 20 per cent chance of prolonged survival.

Several reports in the literature list malignant hypertension as a contraindication to surgical treatment. It is our opinion that malignant hypertension constitutes an indication for splanchnic resection, provided deterioration has not yet advanced to the constitutional extent where surgical treatment has been found to be unavailing.

SUMMARY

This is a study of 143 cases of malignant hypertension, each treated by splanchnic resection. The findings suggest that surgical treatment offers

some hope to the victims of this disease, which usually has been rapidly fatal when treated otherwise.

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PULMONARY BRUCELLOSIS *

By WILLIAM A. HARVEY,† M.D., *New York, N. Y.*

INCREASING recognition of the high incidence of brucella infection throughout Europe¹ and more recently in South America² and the Orient^{3, 4, 5} and especially in certain areas of relatively high endemicity in the United States^{6, 7, 8, 9, 10, 11} is reflected in a professional "brucellosis mindedness" in the tentative diagnostic schema of many physicians. Unsatisfactory laboratory and clinical criteria, however, present a diagnostic problem,^{12, 13} and the imperfection of laboratory aids emphasizes the importance of realizing their limitation and of obtaining as well defined clinical criteria as present experience will permit.

The following case studies present both the diagnostic problem and, in a thus far unrecorded form, the rarely reported clinical manifestation of brucellosis in the lungs, which a review of the literature suggests is a manifestation frequently encountered and unrecognized.

CASE REPORTS

Case 1. A 26 year old American born, married, white nurse was referred to the clinic because of the findings in a chest roentgenogram (figure 1) taken routinely on September 12, 1945 in the course of application for employment. This was described as showing: "Generalized snowflake mottling a little more in the central portion and less in the apices. Perhaps a little more in the right lung, but not appreciably so. No circumscribed calcifications present. Impression: Chronic interstitial fibrosis, etiology undetermined. Miliary tuberculosis and fungus infection to be ruled out."

The patient, who did not believe herself ill, offered no presenting complaints, and these were elicited only in the course of an historical review of systems. Her parents and two siblings are living and well without any recent febrile illness. She was born and lived in Morristown, Tennessee, until the age of 18, when she attended college in Bristol, Virginia, and thereafter, until September 1941, a nurse's training school in Knoxville, Tennessee. Following her marriage the patient lived from September 1941 to November 1943 in the towns of Tunica and Marks, Mississippi. Throughout this period she drank raw milk which in Marks was obtained from a cow kept in "the backyard" of a small apartment house. In this place her husband was in bed for six weeks of the winter of 1942 with a febrile illness, undiagnosed. (He now exhibits a four plus reaction to intradermal Brucellergen, including constitutional reaction with fever.)

The patient recalls no childhood illness except uncomplicated measles at the age of ten. She was well until 1940 when she suffered a pleurisy with effusion which necessitated three weeks of bed rest and the removal of some (undescribed) fluid from the left side of her chest. The etiology was undetermined.

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From the U. S. Naval Dispensary, Washington, D. C., and the laboratories of the National Naval Medical Center, Bethesda, Md.

† Formerly Resident in Medicine at the New York Post-Graduate Hospital, New York City.

At present Assistant Resident Psychiatrist, The New York Hospital.



FIG. 1. Roentgenogram of chest, Case 1, September 12, 1945, showing interstitial fibrosis one year after entire subsidence of respiratory complaints.

The patient's ingestion of raw milk cannot certainly be established before September 1941. About that time she suffered a Bell's palsy which lasted from September 1941 until early 1943. During this time it was noted that she had an irregular fever, ranging about 100° F. The onset of the paralysis was contemporaneous with clinical jaundice which continued for one month. The first evidence of any lymphadenopathy was noted by the patient in the summer of 1942. The patient remarked first the swelling of her cervical glands and "played with them" but states that axillary nodes were also enlarged and, with the cervical nodes, were tender but not painful. The lymphadenopathy has persisted in varying degree until the present, but was greatest in the winter of 1943 which was also the period of greatest febrility and of the beginning of respiratory symptomatology. A "marked hilar lymphadenopathy" is evident in a chest roentgenogram taken routinely in March 1942 (figure 2).

The patient's febrile reaction to her illness was most remarkable through a period of sustained fever throughout 1942 and the first half of 1943. She recorded a daily temperature elevation, usually to 101° F., sometimes higher. Since mid 1943 the fever has been less consistent, the patient noting only a temperature of 100° F. for three to five days at approximately monthly intervals, when prompted to record it because of a

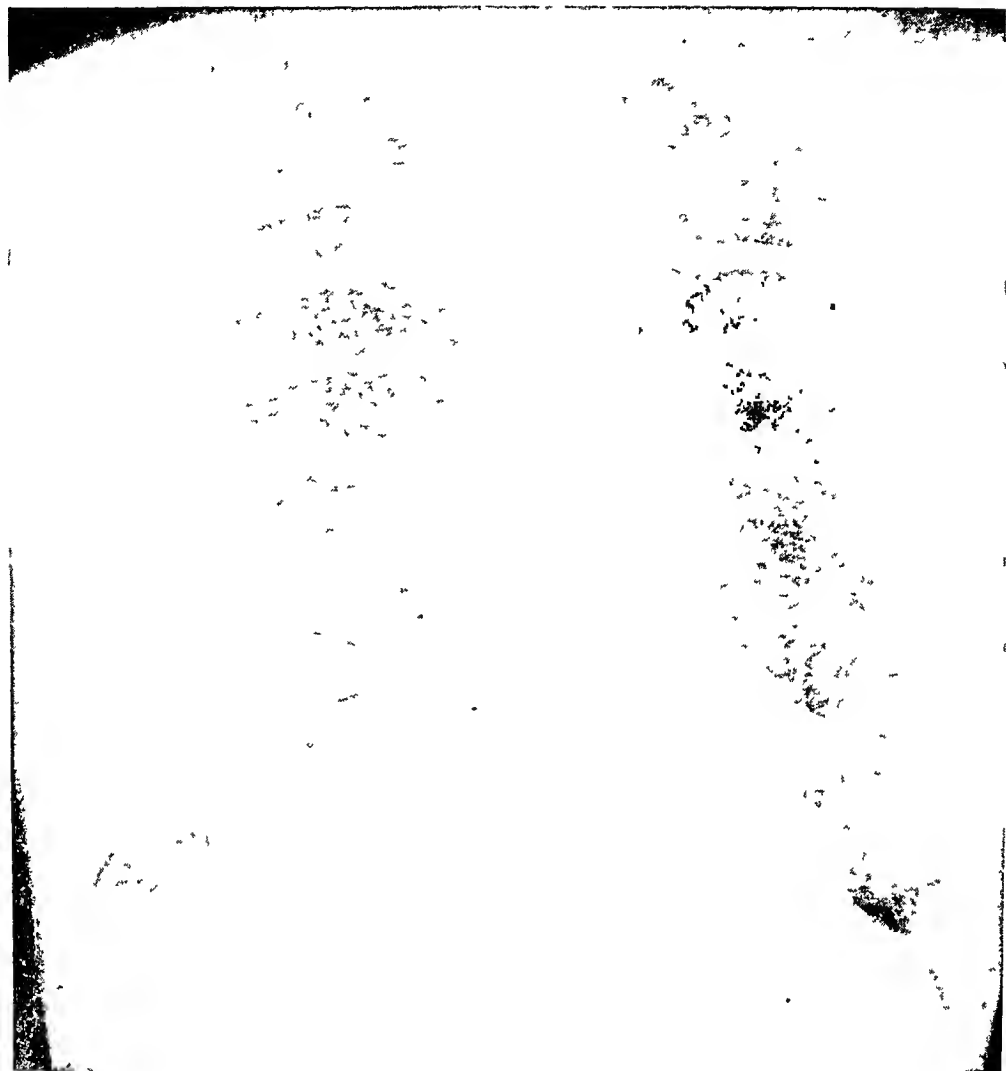


FIG. 2. Roentgenogram of chest, Case 1, showing marked hilar lymphadenopathy in March 1942, ten months prior to onset of respiratory complaints.

"flushed feeling." Malaise, easy fatigability, anorexia, insomnia, and severe calf muscle soreness were her complaints during the period of continued fever.

The patient's respiratory complaints began in January 1943 with a persistent and severe cough productive of one-half to one cupful of yellowish, non-malodorous sputum daily. Her fever and lymphoglandular enlargement were greatest and most consistent at this time. The cough persisted for three months, the patient being up and about attending to household duties. It was associated with sharp chest pain on respiration and on coughing, referred anteriorly and posteriorly, being especially marked along the rib margins. Although the cough largely subsided in March 1943, and the patient has now had no cough at all for at least one year, the chest pain persisted through the spring of 1943. It is still present and is described as a "sore pain," referred retrosternally, on deep breathing. Occasionally there is fleeting and sharp costo-marginal pain.

In the past three years an effort syndrome has been present comprising exertional dyspnea, easy fatigability, perspiration and palpitation on light exertion. For these three years the patient has also had nausea daily, and vomited about twice weekly. She has had some loss of appetite. Her present weight of 124 lbs. is compared to

her best weight of 138 lbs. in 1940. She describes severe joint pains in elbows and knees, without swelling, but with aggravation by movement throughout the winter of 1944-1945.

There is no history of occupational exposure to dusts or to cotton, and no history of any genital infection, nor of any skin sores or ulceration.

Physical Examination. The patient's general appearance was that of an apparently well-nourished, healthy adult young female of hyposthenic habitus. Her temperature was 99° F., pulse 80, blood pressure 115 mm. Hg systolic and 80 mm. diastolic. Skin: There is a seborrhea sicca of the scalp with mild involvement of the facial skin, the skin being otherwise unmarked by scar or sore. Eyes: Consultant notes that "both fundi are normal. Slit lamp examination of anterior segment of both eyes is normal." Nose and throat: Normal. Chest: Symmetrically well developed. No abnormality of breath sounds, tactile or vocal fremitus or of resonance to percussion. Heart: Not enlarged. Sounds of good quality. No murmurs. Normal sinus rhythm. Abdomen: The spleen is enlarged and is palpable, descending two to three fingers'-breadth. Its tip is moderately tender. There is a slight, poorly defined right upper quadrant tenderness to deep palpation. Lymphatics: The anterior cervical lymph glands are enlarged to 0.5 to 1 cm. diameter. Several supraclavicular and right and left axillary nodes are palpably enlarged. All are moderately tender. Pelvis: Negative except for *Trichomonas vaginalis*.

Laboratory Examination. The erythrocyte count was 4.6 million per cu. mm., hemoglobin 12.5 gm. Total leukocyte count was 7,650 per cu. mm. with 68 per cent segmented neutrophils, 3 per cent unsegmented, 26 per cent lymphocytes, 1 per cent monocytes, 2 per cent eosinophiles. The sedimentation rate (Cutler) was reported as 12 mm. per hour, with a maximum settling of 2 mm. in one five minute period.

Blood chemistry: Serum protein 7.1 gm., albumin 4.4 gm., globulin 2.7 gm. Urea nitrogen 11.3 mg. per cent, non-protein nitrogen 34 mg. per cent.

The Kahn test was negative; a smear for malarial parasites was negative.

The urine was alkaline with specific gravity of 1.008, negative for albumin and sugar, contained a few squamous cells and amorphous urates. A catheterized specimen was negative on culture.

Blood agglutination: Positive in 1:80 dilution for *Br. abortus* on three occasions. Negative for *P. tularensis*, *E. typhosa*, and paratyphoid A and B.

The opsonocytophagic test with *Brucella abortus* and the patient's citrated whole blood showed marked phagocytosis in all 25 cells.

Skin tests: Negative after 24 and 72 hours to 0.1 c.c. of Brucellergin intradermally on two occasions. Also negative to 0.1 c.c. of Bacterin (*Brucella* vaccine, 4 million organisms per c.c.). Negative also to intradermal tuberculin, in ascending dosage to 1 mg. O. T. (1:100). Negative to Frei antigen and Coccidioidin. (All skin testing was done after completion of blood agglutination and opsonophagic studies.)

Blood culture: Cultural study of the patient's blood directly and with guinea pig inoculation was on three occasions negative for brucella.

An electrocardiogram was normal. The basal metabolic rate was determined as minus five.

Report of bronchoscopy: "The bronchial mucosa was markedly thickened and granular along the medial wall of the left bronchus from left of the carina to the orifice of the left upper lobe. In one region there was scarring.* Some thickening of the mucosa was also noted in the right bronchus. No obstruction. Impression: Granulomatous lesion, coccidiosis? Cultures taken." The cultures of aspirated sputum were negative for *Brucella abortus*, and negative for pathogenic fungi.

* This description is of interest in view of what has come to be regarded by pathologists¹⁴ as the characteristic lesion of brucellosis: A lymphogranulomatous involvement in which the basic reaction involves the reticulo-endothelial system with a proliferation of large mononuclear cells. This is succeeded by necrosis and then a proliferation of fibroblasts or a scar composed of reticulum.

Roentgenographic study of the patient's chest, hands and long bones on September 27, 1945 was reported: "A teleroentgenogram and stereo examination of the chest shows a normal bony thorax, smooth hemidiaphragms and clear costophrenic angles. Throughout both lung fields from apices to bases, but especially pronounced between the second and sixth interspaces bilaterally, one finds a process involving the interstitial tissues about the terminal bronchioles and apparently causing a marked cellular infiltration and moderate fibrosis. There is no definite alveolar infiltrative process. The pleurae are not affected. Through this feathery change one suspects that the hilar lymph nodes are enlarged bilaterally. The film made two years ago and submitted by the patient shows that this was certainly the case at that time. The trachea is central. Heart and great blood vessels are normal. A definite diagnosis cannot be made on these films. I do not believe this represents a tuberculous manifestation.

"Roentgenographic examination of both hands and of both arms and legs shows no areas suggestive of sarcoid. The bones appear entirely normal."

Three months later, on December 11, 1945, these lung findings were still present (figure 3), and comparison with the previous films showed no change in the appearance of the lung fields.



FIG. 3. Roentgenogram of chest, Case 1, December 11, 1945, showing persistence of interstitial fibrosis.

SUMMARY

This case of a febrile respiratory illness with a clinical onset characterized by prolonged cough, sputum, chest pain and generalized lymphoglandular enlargement, now presents roentgenological evidence of diffuse pulmonary disease without destruction in a patient not apparently ill, whose disease was untreated and is apparently spontaneously subsiding. Earlier roentgenological change is noted in the form of perihilar lymphadenopathy antedating the respiratory symptoms and occurring in a period of prolonged febrility and generalized lymphadenopathy. The lymphoglandular enlargement has largely subsided, splenic enlargement persisting.

The clinical course did not support any of the tentative diagnoses except brucellosis. Other diagnoses were relinquished after consideration of laboratory examinations which excluded the hyperglobulinemia of kala-azar and lymphopathia venereum, the hyperglobulinemia and skeletal changes of Boeck's sarcoid, the hematological findings of blood dyscrasia and of pulmonary actinomycosis,¹⁵ the agglutinations of tularemia, the skin hypersensitiveness of tuberculosis, lymphopathia venereum, and coccidiosis, the presence of any fungi in sputum, or evidence (in a previous roentgenogram) of pneumoconiosis.

*Case 2.** The patient was a 44 year old white housewife admitted March 31, 1946, complaining of a chronic cough. She had been exclusively a resident of New York City since coming to America from her native Austria 25 years ago.

In the early winter, previous to admission, she developed a cough which persisted until the following spring. This cough recurred again at the beginning of winter and continued to the time of admission. The cough was described as irritative, was not productive but was accompanied by a sensation of heaviness and pressure in the chest. There was no dyspnea, no hemoptysis, no weight loss, chills or fever but there was occasional mild night sweating.

Her father had died of a "heart attack" but there was no other history of familial disease. Her mother and three siblings were living and well. The patient's obstetrical history was remarkable in that she was Para VI, Gravida 0. Her last pregnancy ended in 1931, and all the abortions occurred spontaneously at about the fourth month.

A roentgenogram of the chest (figure 4) was described as follows by Dr. William H. Meyer:

"Examination of the thorax shows a slight asymmetry due to moderate rotary curvature of the dorsal spine. The heart is within 10 per cent of limits of normal in relative measurements and contour except for slight straightening of the left heart border.

"There is a considerable degree of hilus, root branch and central bronchial thickening. The latter consists of reticular and spotty peri-bronchial infiltration seen in both central lung fields extending especially toward the terminus of the upper intercostal branches on both sides. The location of the lesion here along with small lymphoid deposits suggests its tuberculous nature of the chronic bronchopneumonic type.

"As stated, the parenchymal infiltration is more marked in the upper lobes but nevertheless is seen somewhat diminishing in extent toward the base, and mainly so on the right side.

* This case was observed during her second admission to the service of Dr. Maurice Bruger at the New York Post-Graduate Hospital.

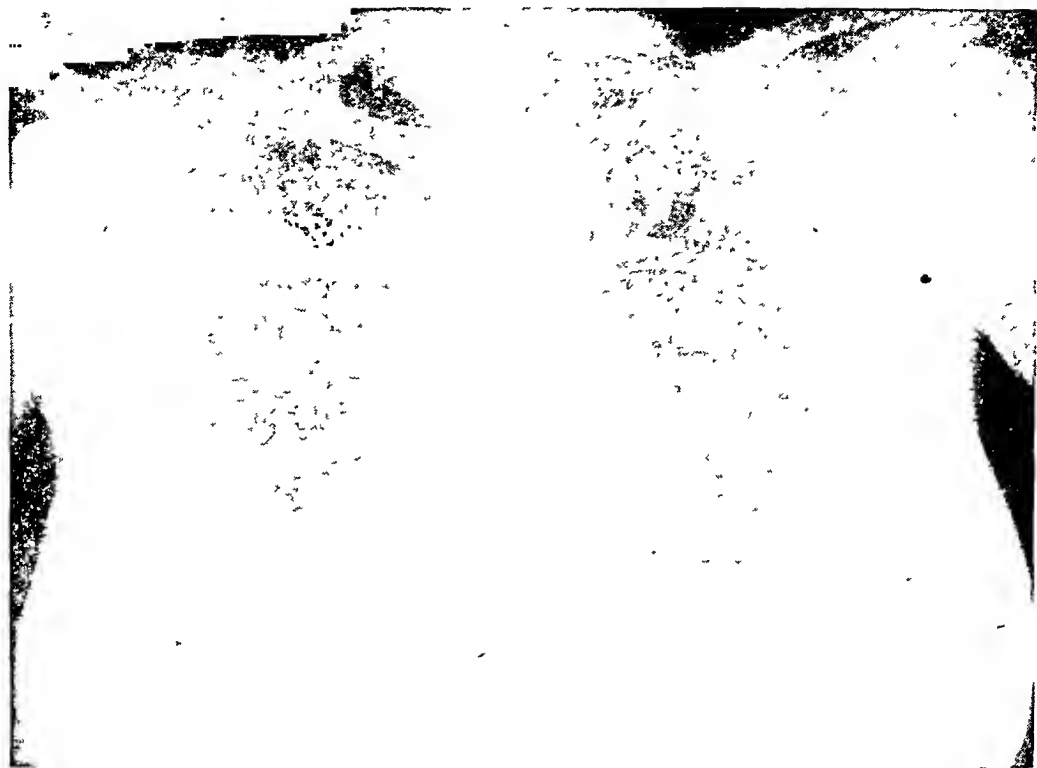


FIG. 4. Chest roentgenogram, Case 2, on first admission, taken April 3, 1946.

"There is moderate concomitant pleural involvement seen both peripherally in the interlobar septum and toward the bases with, however, no evidence of either free or encapsulated exudate.

"Conclusion: Chronic tuberculosis, type bronchopneumonic; infiltration in both lungs, most marked in the upper lobes."

The red blood cell count was 5.05 million with 16.5 grams of hemoglobin. The white blood cell count was 8,450 with 72 per cent polymorphs, 1 per cent eosinophiles, 22 per cent lymphocytes and 5 per cent monocytes. Urinalysis was negative. The sedimentation rate (Westergren) was 12 mm./hr. The Wassermann reaction was negative. Concentrated smears of gastric washings and of sputum were negative for *Mycobacterium tuberculosis*. The patient was afebrile during her hospital stay, being discharged at the end of one week, unimproved, to a sanatorium.

Readmission: The patient was readmitted on August 23, 1946 still with her persistent cough now accompanied by fever. Since discharge she had been at a tuberculosis sanatorium in Denver, Colorado, where she had been studied with entirely negative results except for the roentgenological findings. She was discharged as a "negative case."

For the four weeks prior to admission she had had a low grade fever. She still coughed but stated that she "felt as though there were something there which she could not bring up." There had been no weight loss even on bed rest—in fact, the patient could gain weight easily. There was no pain, hemoptysis or dyspnea.

The physical examination was similar to that of the previous admission except for a temperature elevation to 100.6° F. Afternoon temperature elevations ranging from 100° to 102° were recorded throughout this admission with the pulse rate usually about 100.

A second chest roentgenogram (figure 5) was described by Dr. William H. Meyer:

"Examination of the thorax shows a diffuse reticular and spotty peribronchial infiltration of both lungs. This infiltration is somewhat more marked in the upper lobes and extends well into the parenchyma here. In addition to the bronchial thickening there is a moderate bronchial type dilatation again most marked in the upper lobes. There is a slight degree of pleuritic thickening in the periphery, mainly discernible, however, in the upper septum on the right. There is no evidence of free air or encapsulated exudate. Conclusion: First and foremost a chronic tuberculous type of bronchopneumonic infiltration is to be considered. Far less likely is the possibility of some lymphopathy or obscure reticulo-endothelial lesion."

Intradermal tests with increasing doses of O. T. to 1 mg. were completely negative. Concentrated smears of repeated gastric washings and culture of sputum were

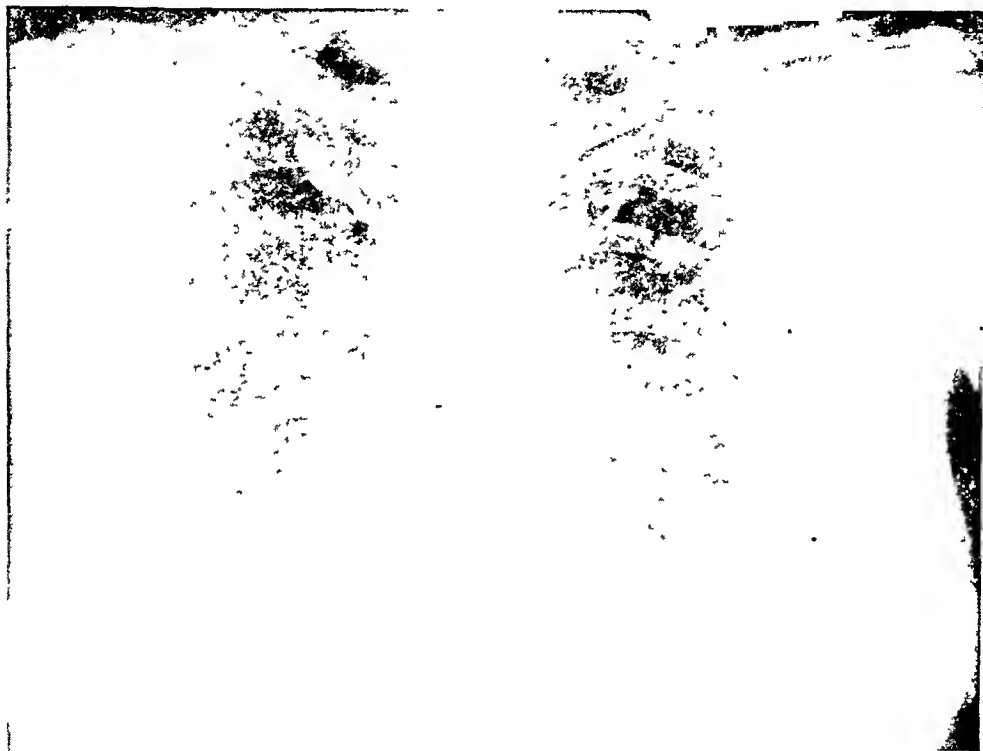


FIG. 5. Chest roentgenogram, Case 2, on second admission, taken August 26, 1946.

reported as negative for *Mycobacterium tuberculosis*. Urinalysis was negative. The red blood cell count was 4.6 million with 14.3 grams of hemoglobin. The white blood cell count was 6,800 with 49 per cent polymorphs, 38 per cent lymphocytes, 12 per cent monocytes and 1 per cent eosinophiles. Sedimentation rate (Westergren) was 26 mm./hr. Four cultures of sputum were negative for fungus. Blood agglutination tests for typhoid and paratyphoid and with *Proteus* X19 and OX2 were negative. The macroscopic agglutination test with *Brucella melitensis* was positive in 1:320 dilution which was the highest dilution used. The macroscopic agglutination test with *Brucella abortus* was strong through 1:1280 serum dilution and slight through 1:5,120 dilution. The Lederle Fegre antigen for brucellosis also gave a positive result through 1:320 serum dilution, the highest dilution used. An opsonocytaphagic index for brucellosis showed 72 out of 100 cells with marked phagocytosis. An intradermal test with 0.1 c.c. of 1:10 dilution of Brucellergen resulted in an area of induration and erythema measuring 2.5 by 1.5 cm. at 48 hours.

Comment: This case illustrates in a manner closely similar to Case 1 the delay encountered in the diagnosis of the infiltrations of the lungs due to brucellosis. In American clinics brucella infection is rarely considered in the differential diagnosis of non-tuberculous pulmonary disease.

DISCUSSIONS

The laboratory findings pertinent to the diagnosis of brucellosis require discussion in these cases which, after a review of the literature, we consider to illustrate a characteristic clinical manifestation of brucellosis.

Recovery of the organism from blood or other body fluids would be the most satisfactory method of establishing diagnosis. In these cases repeated blood cultures were sterile. This is the usual finding in chronic brucellosis,^{12, 13, 16, 17} where most patients are reported negative and where the need for accurate diagnosis is greatest. In the acute disease with proper technic brucella can usually be recovered from the blood or body fluids in a high proportion of cases,^{13, 18, 19, 20} although even here great difficulty is encountered.^{21, 22} The great majority of diagnoses must be based not on culture of the organism, but on the result of other diagnostic procedures. These have significant limitations.

Agglutination of the patient's serum in dilution of 1:80 by *Brucella abortus* was present in Case 1. Serum agglutination in dilution of 1:40 or higher is regarded as "the most reliable indicator of infection."²³ "A positive agglutination reaction is the most accurate indicator of present infection (Dubois and Sollier; Taylor, Lisbonne and Vidal; Meyer and others; Keller, Pharris and Gaub)."²⁴

This is maintained in spite of admitted imperfections: (1) Some strains of brucella are encountered which agglutinate only to low titers.^{7, 13} (2) From 6 to 10 per cent of culturally proved acute cases fail to develop agglutinins,^{7, 13, 17, 19, 25} and in still others agglutinins appear only in the acute phase,^{13, 17, 19, 25, 26, 27} or only in recovery,^{25, 27} or intermittently.^{13, 17, 25} (3) The agglutination test is frequently negative in the presence of chronic disease.^{7, 11, 28, 29} (4) Cross agglutination with *P. tularensis* occurs.⁷ The significance of positive agglutination in the diagnosis of present disease must of course always be adjudged in the light of clinical history and findings. The high degree of reliability of this test is emphasized by the studies of Shaughnessy.³⁰ Carpenter and Chapman³¹ have established that anti-*abortus* agglutinins develop only when there has been an actual invasion of the tissues by living brucella organisms.

The failure of any reaction to intradermal injection of Brucellergen and Brucellin was noted in Case 1. This is not unusual in the presence both of acute^{19, 21, 25, 27, 32, 33, 34} and chronic disease.^{13, 22, 27, 32} The skin test is an unreliable test of infection in brucellosis.^{7, 35} There is general agreement that cutaneous hypersensitivity indicates previous contact, not necessarily clinical illness.^{13, 25, 27, 32} Cutaneous hypersensitivity in brucellosis develops later

than agglutinins.⁷ All evidence points to the error of Gould and Huddleson's statements that "all individuals who have been infected with brucella as well as those who are actively infected will show an allergic reaction to a satisfactory brucella antigen,"³⁶ and that "if the brucellergen test is negative, brucellosis may usually be ruled out."¹¹ Evans found the incidence of negative skin tests in the presence of chronic infection to be as high as 39 per cent.⁷ And it should be noted that a study by Huddleson's group put the incidence of negative reactors at 5.5 per cent.⁶

Huddleson has offered the opsonocytophagic power of citrated whole blood for brucella as a diagnostic aid and states further that "it is an expression of immunity to brucella and an indication of the progress toward recovery in active infection."³⁶ Its value in diagnosis has been confirmed by other studies,^{11, 13, 17, 37, 38, 39} although Evans and her co-workers question its reliability as an index of immunity "for we found strong positive reactions in patients with chronic brucellosis and weak or moderate reactions in recovered cases."⁷ Tovar offers the same objection.⁴⁰

In the absence of a positive culture it would appear that the diagnosis is not established to general satisfaction unless two of the specific laboratory tests are positive,¹³ although there are many published reports in which the diagnosis has been accepted on the basis of positive skin test alone,^{22, 41} or of positive agglutination alone.^{22, 41, 42, 43}

Pleurisy^{6, 17, 43, 44, 45, 57} and bronchitis^{43, 44, 46} are familiar to students of brucellosis. This type of parenchymal pulmonary involvement is not familiar. Very few are the reports of any variety of pulmonary involvement attributable to brucellosis and most of them are in the European literature. Markoff⁴⁷ in 1940 thought it could be stated that "the pulmonary form of the disease does not exist in North America." However, Johnson,⁴² Bogart,⁴¹ Lafferty and Phillips,⁴⁹ and Beatty⁴⁶ had recognized this form of brucellosis, although Johnson admits the diagnosis on the basis of agglutination alone, and Bogart on the basis of skin test alone or agglutination alone. Johnson and also Bogart describe perihilar and peribronchial infiltrations, spontaneously resolving. Beatty,⁴⁶ although not presenting his diagnostic criteria, studied 12 cases of undulant fever with respiratory symptoms and described the roentgenological findings as consisting of hilar infiltration, peribronchial infiltration, thickened pleura, pleural adhesion and pleural effusion. Sidel and Segal⁵⁰ reported a case simulating pulmonary tuberculosis with "suspicious x-ray findings" which were not enumerated and which subsided spontaneously.

The European literature also contributes to the description of a fairly characteristic course in pulmonary brucellosis with perihilar lymphadenopathy, an initial bronchitis or pneumonitis of prolonged duration and usually with spontaneous resolution. Markoff⁴⁷ reports three cases all with hilar gland swelling and perihilar infiltration similar to the hilar gland enlargement described by both Bogart and Johnson with eventual clearing. Arroba-Juzgado²¹ described in 1936 the study of a patient presenting perihilar lymph

phadenopathy associated with generalized lymphadenopathy in whom skin and blood agglutination tests were negative but with *Brucella melitensis* finally recovered from the blood. His patient had a lymphocytosis such as is found in about one-half of the acute brucella infections.⁵¹

Markoff^{47, 48} emphasizes the importance of the initial bronchitis. The severity and prolonged clinical course of the bronchitis of brucellosis is remarked on by Johnson whose three cases required 14 to 17 weeks for recovery. Bethoux⁴³ also mentions the prolonged duration of bronchitis in brucellosis, reporting cases of four and five months' duration and emphasizes the predominance of pulmonary symptoms with minimal physical signs, suggesting that this may be due to the observed tracheo-bronchial adenopathy.

Slow resolution with ultimate recovery was noted by Harris¹⁷ in reporting the roentgenological findings in two cases of brucella pneumonia. Bronchopneumonia in brucellosis is also reported by Markoff,^{47, 48} Bethoux,⁴³ Bjurström,⁵² Curschmann,⁵³ Kristensen and Holm,⁵¹ Attinger,⁵⁵ Greichner,⁵⁶ and Bolaffi.⁵⁷ The morbid anatomic changes are described by Sprunt and McBryde.⁵⁸ Bjurström's case was one of pneumonia with bilateral pleural effusion which yielded the organism on culture. Vedel, Puech, and Vidal²⁰ report spontaneous resolution of a pyopneumothorax in brucellosis. Acute brucella empyema not requiring surgery has been reported by Macdonald.²⁰

Besides the early perihilar involvement and the peribronchial infiltration, both of the cases here reported showed evidence of persistent fibrotic changes. The tendency to fibrosis in pulmonary brucellosis has been previously observed by Lafferty and Phillips⁴⁹ who described in three cases a prolonged clinical course of respiratory symptomatology with roentgenological evidence of "rapidly progressive fibrosis" succeeding the "peribronchial congestion, or rather diffuse bronchopneumonia." Bogart,⁶⁵ in the discussion of the same paper, adds the testimony of his experience, stating that the tendency of the infiltration to be quickly absorbed "does not always occur, as I have seen some cases which have undergone gradual absorption and fibrosis over a period of one to two years."

Di Pace⁴⁴ in relating three cases of bronchitis in brucellosis discusses the question whether it represents actual invasion of the tissue by the organism. In this connection Huddleson⁵⁹ states regarding brucellosis in Malta that "pulmonary complications are due to secondary invasion as it has been impossible to recover *Brucella melitensis* from the sputum." This has been a prevailing impression regarding the disease in this country. Nevertheless, sputum^{17, 60} and pleural^{52, 61} and empyema²⁰ fluid have yielded brucella when looked for, in a number of studies since Eyre in the 1908 Milroy Lecture⁶² first gave Fiorentini credit for isolation of the organism from the sputum in bronchopneumonia.

Bethoux⁴³ as well as Harris¹⁷ point out the ease and frequency with which the disease, "*la phthisie méditerranéenne*," simulates tuberculosis and is mistaken therefor. The need for reëvaluating our concept of brucellosis as it affects the lung is well illustrated by the experience of Hardy who wrote

in 1929⁶³ of a series of 125 cases of undulant fever that "a cough was only occasionally present." Then in the following year stated, "More careful records in our later series of 175 cases indicate that more than one-third of the patients had a cough, some with mucoid or mucopurulent sputum."⁶⁴ Careful reporting should eventually define what part of the non-tuberculous infections of the lung are caused by brucellosis.

CONCLUSION

1. Two cases of chronic diffuse pulmonary disease due to brucellosis are presented.

2. A review of the literature suggests that these are instances of a characteristic clinical course in pulmonary brucellosis marked by perihilar lymphadenopathy, bronchitis or pneumonitis of prolonged duration and usually spontaneous subsidence with resorption or fibrosis, all of which stages have been separately reported in previous studies.

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WAR EDEMA IN THE CIVILIAN POPULATION OF SAIPAN*

By N. B. KURNICK,† M.D., *New York, N. Y.*

REPORTS on hunger edema were published many centuries ago. Diogenes Laertius described the fate of the philosopher Heraclitus (born ca. 435 B.C.) who, despairing of his fellow man, withdrew to the hills as a hermit. Here he subsisted only on herbs, became dropsical and died. Since then, recorded history reports the frequent recurrence of epidemics of edema in periods of famine.¹ The condition particularly attracted the attention of the medical profession in Central Europe during its outbreak in the First World War, when it became known as "War Edema." These observers were the first to appreciate the importance of the dietary factor in the etiology of this disease. They excluded infectious factors and considered avitaminosis unlikely in the etiology. Knack and Neumann,² Lippman,³ and Schittenhelm and Schlecht⁴ were the first to carry out serum protein determinations on patients with war edema (by refractometric methods). They found the values to be consistently reduced. These authors suggested, therefore, that protein deficiency in the diet might be the etiological factor. The observation that serum protein concentrations are regularly reduced in nutritional edema has received wide confirmation.^{5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22} Kohman²³ demonstrated experimentally that diets inadequate only in protein resulted in edema in rats, and that the simple addition of protein prevented the disease. Frisch, Mendel and Peters²⁴ repeated her experiments and demonstrated a reduction in plasma proteins in the edematous animals. These findings made it appear probable that nutritional edema was due to the reduction in the colloid osmotic pressure of the plasma secondary to the reduction in serum albumin, as would be predicted from Starling's theory.²⁵ Leiter²⁶ produced edema in dogs by effecting a reduction in plasma proteins by plasmapheresis. Starling's theory thus became generally accepted as satisfactorily explaining the pathogenesis of nutritional edema.^{5, 27, 28, 29, 30, 31} A total protein of 5.0 to 5.5 grams per hundred c.c. and an albumin concentration of 2.5 to 3.0 grams per hundred c.c. was considered to be the critical level below which edema was to be expected.^{22, 32, 33}

The principal problem that remained for the clinician was to distinguish protein deficiency edema from that due to vitamin deficiency. Some authors deemed it not unlikely that war edema represented a mild form of beriberi, and as a matter of fact low serum protein levels have been reported as a characteristic finding in beriberi.³⁴ Part of the edema observed in some patients

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From the Laboratory of the 369th Station Hospital, Saipan, M. I.

† With the technical assistance of Mr. B. Slotiuk. Present address, The Rockefeller Institute for Medical Research, New York, N. Y.

on deficient diets may well be attributed to cardiac failure due to vitamin B₁ deficiency, while associated protein deficiency may contribute to the accumulation of fluid in the tissues. The arguments against vitamin B₁ deficiency in most outbreaks of war edema are:

1. The failure to detect any cases of frank beriberi in large epidemics.
2. The preservation of normal reflexes in the patients with war edema (whereas in Hong Kong, where beriberi was a common finding, diminished reflexes were almost constant, even in subclinical cases).³⁵
3. The bradycardia and diminished heart size and cardiac output (as opposed to the tachycardia, cardiomegaly, congestive failure, and increased cardiac output of beriberi).^{36, 37}
4. The failure of the patient to respond to massive vitamin therapy.^{4, 38}
^{39, 40}

Simonart,⁴¹ however, reported relief of edema and increase in serum protein concentration after vitamin B therapy. He used brewers' yeast as the source of vitamin B. Brull³⁸ has demonstrated that yeast is a readily assimilated source of nitrogen. Brull and his collaborators³⁸ and Crismer⁴² carried out extensive studies of vitamin content and excretion tests in patients with war edema during the recent German occupation of Belgium and France. They discovered no evidence of vitamin deficiency in their cases. Brull found the average serum protein concentration normal in the non-edematous population of Belgium, while that of the edematous group was about 4.5 grams per cent. Harden and Zilva⁴³ demonstrated experimentally that monkeys fed on a beriberi producing diet of polished rice, developed edema but no neuritis if vitamin B₁ was added.

MATERIAL

About three months after the invasion of Saipan, the hospital admissions to the civilian hospital began to include a large number of patients with peripheral edema, some of whom also had ascites and hydrothorax. Most of these patients complained of muscular weakness, characterized particularly by difficulty in arising from the customary squatting position. These findings were suggestive of the neuritis and edema of beriberi. However, examination revealed that the reflexes were normal, that there was no evidence of cardiac failure, and that findings indicative of other vitamin deficiencies were lacking. Large doses of thiamine, parenterally, were without effect. It was the impression of the author, therefore, that these cases probably represented nutritional edema due to protein deficiency rather than to avitaminosis. Therefore, the following study of serum proteins was undertaken (table 1). The copper sulfate method of Phillips, Van Slyke, et al.⁴⁴ was used, as the most readily applicable under field conditions.

The subjects had been living in the hills or in an internment camp on a diet consisting of rice, a few greens, onions, and about an ounce of fish daily.

TABLE I

Serum Proteins gm./100 c.c.	2.5-3.0	3.1-3.5	3.6-4.0	4.1-4.5	4.6-5.0	5.1-5.5	5.6-6.0	6.1-6.5
Patients with edema October 1944	1	1	3	2	9	2		
Patients with edema November 1944	2	5	4	12	16	12	8	7
Total patients with edema	3	6	7	14	25	14	8	7
Orphans November 1944						2	7	3

Serum Proteins gm./100 c.c.	6.6-7.0	7.1-7.5	7.6-8.0	Total	Less than 5.5	Over 6.5	% Over 6.5	% Less than 5.5
Patients with edema October 1944			1	19	18	1	5.3	94.7
Patients with edema November 1944	3	1		70	51	4	5.7	72.9
Total patients with edema	3	1	1	89	69	5	5.5	77.5
Orphans November 1944	16	13	1	42	2	30	71.4	4.8

The 42 orphans who served as controls lived at the orphanage maintained by the Military Government, and fared slightly better. At the time of these analyses, none of these children had edema. Fifty determinations on normal U. S. Army troops revealed serum protein values of 6.5 to 8.9 grams per cent.

As was noted above, none of the patients responded to thiamine therapy. The death rate was very high. One hundred of those who died were examined post mortem by Drs. Klosterman, Hirsch, and the author. Malnutrition was constant and advanced pulmonary tuberculosis was very common. (The high incidence of tuberculosis in the malnourished was noted also by Leyton in Russian prisoners of war.⁵) In no case were gross or microscopic changes consistent with beriberi found. The heart was normal, or small in all except one case. Those who survived became free of edema over a period of several weeks on the improved hospital diet. Unfortunately, there was no opportunity to follow the course of the serum proteins as the edema improved nor were facilities available for thiamine determinations.

DISCUSSION

Examination of the table reveals a definite grouping of edematous patients in the markedly subnormal range for serum proteins. In the small series studied during October (19 cases) only one had a normal serum protein level.

In the larger series of 70 cases studied in November, only four were in the normal range. Among clinically well native children, less than 5 per cent had serum protein levels below the "critical level for edema" (5.5 gr. per 100 c.c.) and none had a serum protein concentration below 5.1.

It may well be that if serum albumin and globulin had been determined separately, an even better correlation between the incidence of edema and protein levels would have resulted. The colloid osmotic pressure of albumin, as is well known, is four times greater than that exerted by an equal concentration of globulin. Serum globulin in nutritional edema appears usually to have been normal or slightly increased in most series.^{6, 8, 9, 10, 20, 21, 22, 33, 38} Furthermore, intercurrent infections in many of our cases may well have contrived to increase the serum globulin, thereby masking the hypoalbuminemia. Tuberculosis, syphilis and yaws, all of which tend to elevate serum globulin levels, were extremely common. Positive serological tests (Kahn) were found in 56.3 per cent of the Chamorros, 40.0 per cent of the Koreans, and 26.7 per cent of the Japanese examined (986 examinations evenly distributed among the three groups).⁴⁵

Intestinal helminthiasis (*Strongyloides*, hook-worm and *ascaris*) was universal. This may have contributed to the protein deficiency.

Vitamin B₁ deficiency seems to have been excluded on clinical grounds. We concluded therefore, that the edema of our patients was adequately accounted for on the basis of hypoproteinemia alone.

CONCLUSIONS

Our results lend support to Starling's concept of the factors involved in edema formation. It is of interest that several observers have recently challenged the rôle of hypoproteinemia in the pathogenesis of war edema. Chief among these are Keys and his co-workers,⁴⁶ who subjected 34 healthy volunteers to prolonged protein deprivation. They found that edema occurred in almost all in two to six months, while the serum proteins were reduced by only 0.73 gram per cent (average). They considered the consequent reduction in osmotic pressure to be insufficient to account for the development of edema. Others have felt that the simple explanation of reduced colloid osmotic pressure was inadequate, since it failed to account for the approximate 10 per cent of cases of nutritional edema with serum proteins within the normal range.⁸ Most of these authors prefer to consider a neuro-hormonal imbalance to be at fault.^{9, 47, 48} They point to the bradycardia, lowered basal metabolic rate, marked hypoplasia of the thyroid, and polyuria as evidence. They consider the subsidence of edema in many cases simply on bed rest, without concomitant rise in the serum proteins, and the fluctuation of edema with changes in salt and water intake, as points at variance with Starling's formulation. Gounelle and his collaborators^{9, 48} object to the causal relationship of reduced colloid osmotic pressure to edema because they failed to find reduction in serum protein in the phase preceding clinical edema.

However, during edema, they consistently found the serum protein concentration to be reduced as compared to the preclinical phase. Laroche and his co-workers⁴⁹ found a reduced serum cholesterol in their patients and suggested that this might be significant in the pathogenesis of edema. However, others have found normal cholesterol values in most of their patients.^{6, 7, 22, 38} Brull³⁸ suggested that a direct renal and cardiac influence resulting from the protein deficient diet contributed to the edema, but admitted that the reduction in serum proteins was the most important factor. His work indicated that the kidney of a malnourished dog, when transferred to the neck of a normal dog, functioned less adequately than the similarly transplanted kidney of a normal control animal. Loeper et al.⁵⁰ agree that lowered osmotic pressure is found in most cases, but argue that this may be a result rather than the cause of the morbid state. They consider neuroglandular causes, and increased capillary permeability and fragility more likely etiological factors.

We are loath to dismiss so simple and convincing a scheme as Starling's theory affords. We believe that by regarding the conditions as dynamic rather than static, we can account for the discrepancies alluded to. We may state the factors at play in determining the transudation of fluid across the capillary membrane by the following formula, which represents the conditions at equilibrium, neglecting lymphatic drainage:

$$P_a + COP_t - COP_p - P_t = COP_p + P_t - COP_t - P_v,$$

P_a , P_v represent the blood pressure against the wall of a capillary at its arterial and venous ends, respectively;

COP_t , COP_p represent the colloid osmotic pressure of the tissue fluid and plasma respectively;

P_t represents the pressure of the tissue fluid.

The left side of the equation states the conditions favoring transudation of fluid into the tissue spaces at the proximal end of the capillary; and the right half states the conditions favoring resorption of fluid at the venous end.

If, now, we were to disturb the equilibrium by reducing COP_p , the effect would be to favor transudation and oppose resorption. The resulting movement of fluid will quickly reestablish equilibrium, since the loss of protein-free fluid from the blood will tend to raise COP_p toward its original level and to increase P_t . Examination of the blood at the new equilibrium, in which edema now exists, may reveal no significant hypoproteinemia. Hemoconcentration should, however, be apparent. Studies on patients with war edema reveal normal or elevated red counts and hemoglobin in the absence of iron deficiency.^{4, 38, 47} Lippman³ described the "paradoxical" behavior of the red count and hemoglobin in that they were higher during the edema than after its subsidence. This may be taken as evidence of hemoconcentration. Brull³⁸ found that dogs maintained on protein free diets developed increased total plasma volume as well as total body water, while the relative red-cell

volume tended to rise slightly. During the course of his experiment, the dogs lost a considerable amount of weight. If the values are recalculated to give absolute values instead of being expressed as c.c. per kilo as Brull did, a typical experiment reveals a total plasma volume of 435 c.c. before the experiment and 391 c.c. after the protein deprivation. Chang¹⁷ found that his patients with nutritional edema had reduced plasma volumes, although the water content, expressed in c.c. per 100 c.c. of plasma, was increased due to the reduction in plasma proteins. Keys⁵¹ found that the average plasma volume in his 34 normal starved males rose from 45.6 to 64.0 c.c. per kg. body weight, while the average body weight fell 17 kg. Assuming an initial average weight of 70 kg. we find that, as in Brull's experiment, the average total plasma volume actually fell from an initial level of 3192 c.c. to 2352 c.c.

If, on the other hand, P_a and P_v were increased, as by prolonged standing or sitting without exercise, the tendency to filtration would be increased and to resorption decreased. The loss of fluid would elevate COP_p above normal and increase P_t to reestablish equilibrium. That edema of the legs occurs in normal persons on prolonged standing or sitting without muscular activity is a common observation (as in the refugees of the present war after extensive train travel).³⁸ Thompson, Thompson and Dailey⁵² and later Youmans et al.²⁹ determined plasma proteins in normal subjects in the erect position and found that they were significantly elevated, as predicted by our formula. Carles³⁸ has shown that the diminished renal output which occurs in the erect position may be prevented by wrapping the legs firmly with an elastic bandage. The effect of this procedure would be to increase P_t , thereby preventing transudation of fluid.

The effect of excessive hydration or dehydration on subjects with low serum proteins is also apparent from the equation. The ingestion of salt and water will tend to correct the hemoconcentration described above, thereby lowering COP_p and thus aggravate the edema. Dehydration would have the opposite effect. In both cases reestablishment of equilibrium tends to return COP_p toward normal so that analyses may fail to reveal any significant change.

Likewise, bed rest of the edematous patient lowers the blood filtration pressure (P_a and P_v) in the dependent portion of the body (where edema fluid accumulates) thus permitting the factors which favor resorption to "drive" fluid back into the circulation whence it is excreted by the kidneys. The same factors which favor transudation favor renal filtration, which may account for the polyuria and polydipsia noted by many authors.^{4, 5, 38, 46, 53, 54, 55}

Just as the normal range for plasma protein concentration is a fairly wide one (6.5 to 8.9 per cent in our series), so the level at which edema will occur must be wide, since, as we have demonstrated, transudation is a dynamic process and may become clinically evident as edema even when the resultant colloid osmotic pressure is not considerably reduced from the normal. However, it may be stated that the usually accepted "critical level" for edema (total protein of 5.5 plus or minus 0.3 gram per cent, and albumin 2.5

plus or minus 0.2⁸²) will apply to most cases, since at this level all compensatory mechanisms seem to be without avail²⁷ and transudation stops only when sufficient edema fluid has collected to increase P_t appreciably at which point it is readily apparent clinically.

Govaerts and his co-workers^{56, 57, 58} have found, by osmometric determinations on the serum of patients with famine edema, that the colloid osmotic pressure was, on the average, lower than would be expected from calculations based on the formula of Govaerts⁵⁹ and Schade and Clausen.⁶⁰ Govaerts⁵⁸ suggested that this discrepancy is accounted for by the production of abnormal proteins in famine, as is indicated also by the abnormal arginine: lysine ratio,^{61, 62} the shift in the curve of protein precipitation by phosphate solutions,⁶³ and the slight shift among the globulins in the Tiselius electrophoretic pattern.⁵⁷ Govaerts^{56, 57, 58} found the plasma proteins within the normal range in three, and the colloid osmotic pressure normal in only one (normal range of total protein 7.0 to 9.0 gm. per 100 c.c. and of colloid osmotic pressure 35 to 40 cm. water) of 75 subjects. The average colloid osmotic pressure was reduced to 60 per cent of normal, while the average serum protein concentration was 78 per cent of normal. Twenty-seven determinations revealed total proteins above 5.5, but only three patients had colloid osmotic pressures above the "critical level for edema" (30 cm. water).⁵⁹ The colloid osmotic pressure rose only insignificantly with the subsidence of edema on bed rest from an average of 25.6 to an average of 28.5 cm. of water. Thus, whereas Govaerts' findings explained many of the apparent discrepancies with Starling's theory in cases of famine edema, the considerable number of patients with only slight reduction in colloid osmotic pressure, and the subsidence of edema without significant rise in osmotic pressure remained to be explained. These, we believe, are accounted for in the dynamic formulation we have presented.

We are, therefore, of the opinion that nutritional edema, such as was observed in our cases, is due to hypoproteinemia and that the resultant reduction in colloid osmotic pressure, even though transient and inapparent in many instances, accounts for the principal symptomatology of this disease.

SUMMARY

1. Serum protein determinations were performed on 89 edematous and 42 non-edematous patients who had subsisted on a deficient protein intake.
2. The results indicate that hypoproteinemia was an almost constant finding in the former group. Total protein values as low as 2.5 gm./100 c.c. were noted. Beriberi was excluded on clinical grounds.
3. The pathogenesis of war edema is discussed. Starling's theory of the factors governing transudation appears to account for the findings. The deficient diet is believed to provide insufficient protein for the regeneration of serum proteins, resulting in a decrease in the plasma colloid osmotic pressure. Since transudation is a dynamic process, the reduction in serum protein concentration may not be appreciable even with clinical edema.

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GYNECOMASTIA FOLLOWING SEVERE STARVATION *

By EUGENE C. JACOBS,† Lt. Col., M.C., A.U.S., *Washington, D. C.*

I. INTRODUCTION

By definition gynecomastia¹ is "Excessive size of the male mammary glands." By common usage gynecomastia is composed of true and false types.² True gynecomastia consists of hyperplasia of the rudimentary mammary ducts and of the periductal connective tissue. False gynecomastia is a proliferation of fatty and subcutaneous tissues. This paper pertains only to true gynecomastia and purposely is not titled "Gynecomastia due to severe starvation," the reasons for which will appear later.

II. SEVERE PROTRACTED STARVATION

During 40 months of incarceration by the Japanese, all of the known vitamin-deficiency diseases became prevalent. During the first eight of these months, 2400 of the 9000 American prisoners at the Cabanatuan Prison Camp died, the deaths being due primarily to inanition and associated vitamin-deficiency diseases.

The diet consisted of 200 grams, more or less, of a very poor grade of rice, and greens, made from weeds. Once or twice a week, a carabao (water buffalo) was killed for meat. Fruits and vegetables in very small quantities were available to the few prisoners who had brought money into camp, and those who worked on the farm. The daily diet averaged from 800 to 1200 calories, about 60 calories being protein and the rest carbohydrate. The diet was practically devoid of fat.

After two years (four months in combat; 20 months in prison camp) of starvation, each prisoner received four Red Cross parcels. The parcels weighed 11 pounds each, and contained largely canned foods. Using these foods to supplement the regularly issued diet, there was adequate food and vitamins for a period of three to four months. After that the diet again became insufficient, and remained such until liberation 22 months later.

III. TRUE GYNECOMASTIA

Three weeks after the arrival of the Red Cross food, a white male of 23 years complained of a painful, swollen breast. There had been no history of injury. A malignancy was suspected by the surgeon, Colonel William D. North, M.C., U. S. Army, and the breast was promptly removed. Within

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† Associate, American College of Physicians. Office of the Surgeon General, U. S. Army. Formerly Chief of Medical Service, Japanese Prisoner of War Hospital, Cabanatuan, Philippine Islands.

a week a second case appeared, and it was likewise resected. Although the pathologist, Captain Robert Lewis, M.C., U. S. Army, was unable to make sections of the tumors because of inadequate equipment, he reported that the gross specimens appeared to be gynecomastia. Since liberation, the pathological diagnosis has been verified many times.

Within a few weeks some 300 cases were observed in the hospital. It was estimated that at least another 300 cases existed in the camp, but were not severe enough to be reported. Approximately 10 per cent of the prisoners in camp were involved. Four per cent were advanced cases; 6 per cent were mild.

The ages of those developing gynecomastia varied from 18 to 64 years. Forty-six cases (15 per cent) gave a previous history of gynecomastia at puberty. An Army sergeant, aged 64 years, stated that this was his third experience with painful swollen breasts. He had had gynecomastia at puberty, and again after a long serious illness.

At least 50 per cent of the cases were bilateral, although it was usual for one tumor to precede the second by from one to eight weeks. The tumors consisted of smooth subcutaneous disks of firm tissue, attached at the centers to the nipples. Because of the absence of fat, the tumors could be readily palpated, and even picked up from the chest wall and moved from one to two centimeters. They varied in size from one to five centimeters (average 2 cm.). Ninety per cent were tender, some so sensitive that clothing could not be worn against them. Fifty per cent of the patients complained of constant pain, likened to a painful cellulitis. In nine cases (3 per cent) a secretion, similar to colostrum of parturition, was present. This was bilateral in two cases. In one case the secretion appeared to be milk.

In none of the cases was a definite history of injury obtained. After the gynecomastia had become established, however, because of its marked sensitiveness, any external pressure produced extreme pain, and was occasionally mistaken for an injury.

The tumors reached a maximum size in one to eight weeks, and remained stationary until they spontaneously disappeared in from one to 24 months (average four months). None showed any tendency to grow after their size had once become stabilized. None became nodular or lobulated. None became malignant during observation (22 months).

Because of the vast number of vitamin deficiency diseases, it was natural to attempt to explain the tumors of the breasts on a deficiency basis, but it was noted that the tumors had not developed during starvation. They appeared several weeks after the diet had become adequate^{3,4} when other deficiency diseases were disappearing. And then as the diet became inadequate again, the tumors slowly became painless and disappeared, while the deficiency diseases slowly reappeared. No new cases of gynecomastia were observed during the next 20 months,⁴ while the diet was again minimal and barely compatible with life.

After liberation and a sudden return to an adequate American diet, the prisoners literally gorged themselves for a matter of weeks. Weight gains of from 10 to 15 pounds a week were common. Within three to four weeks after the diet became adequate, cases of gynecomastia appeared. Many prisoners who had not previously developed gynecomastia following the issue of Red Cross parcels were now affected. It is estimated that nearly 50 per cent of the returning prisoners-of-war of the Japanese had some degree of gynecomastia on return to the United States.

Since there was great anxiety on the part of the prisoners to see their families and homes, which they had been dreaming of for 40 months, many of the tumors were minimized and as a result overlooked. In spite of this, several Army General Hospitals collected sizable series of cases^{3, 4, 5} of gynecomastia among the recovered prisoners.

IV. CAUSES OF GYNECOMASTIA

In attempting to determine the cause of gynecomastia following starvation, it is natural to review the already established causes² of gynecomastia:

1. Males at puberty² frequently develop gynecomastia. It is rather well established that this condition is a result of a temporary imbalance of the sex hormones, a deficiency of androgen due to hypogonadism, or a relative increase of estrogen. Most of the tumors disappear spontaneously within a few months, as the sex hormones assume their normal relationship. Most of these tumors disappear promptly with a few injections of testosterone.

2. Atrophy of the testicle from any cause (roentgen-ray, mumps, injury, tuberculosis, syphilis, malignancy, orchitis, varicocele or undescended testes) or orchidectomy lowers the androgenic function, predisposing the individual to gynecomastia. Again injections of testosterone cause many of the breast tumors to disappear, leaving no residuals.

3. Estrogen-producing tumors in the male at any age may result in gynecomastia. Examples are: chorioepithelioma, teratoma and interstitial cell tumor of the testicle; hyperplasia or tumor of the cortex of the adrenal; or adenoma of the pituitary.

4. Pseudohermaphroditism is frequently associated with gynecomastia due to insufficient androgenic function. By supplying testosterone, the gynecomastia can frequently be relieved and the male secondary characteristics accentuated.

5. Cirrhosis of the liver is often associated with gynecomastia, apparently because of impaired liver function. The diseased liver is unable to inactivate estrogen, resulting in increased or relatively increased estrogen levels.

6. Estrogen-treated diseases such as migraine occasionally result in typical gynecomastia.

7. Injury is occasionally blamed for gynecomastia, but an accurate history usually reveals that the tenderness of the breast was already present when the alleged injury took place.

8. Other conditions, such as leprosy, have been reported in association with gynecomastia, but the reason for it is not understood.

Summarizing the above causes, it is apparent that gynecomastia is closely associated with a decrease in the androgenic function or level, an increased estrogenic function or level, or both. It also appears that a reduction of the increased estrogen level or an increase of the lowered androgen level causes many of these tumors to subside. However, cases that are neglected or untreated for months or years do become fixed, and fail to respond to large doses of testosterone.

V. DISCUSSION OF THE GYNECOMASTIA ASSOCIATED WITH STARVATION

Starvation causes a decrease of sex hormone production^{4, 6} directly by action on the gonads and indirectly by decreasing the gonadotrophic function. Estrogen and androgen levels are both decreased. Following protracted starvation, an adequate diet for several weeks or months stimulates sex hormone production directly by action on the gonads, and indirectly by increasing the gonadotrophic function. If no other factors were involved, estrogen and androgen levels would become normal.

However, there are other factors. Normally, the liver inactivates any excess of androgen and estrogen,^{7, 8, 9} which tends to keep the levels and ratio normal. When the liver has been impaired by starvation, it becomes unable to inactivate estrogen,^{7, 8, 9} but can still inactivate androgen.⁹ As long as the starvation continues, there is no or very little excess of estrogen, because of the diminished production of estrogen. When the diet subsequently becomes adequate, however, estrogen as well as androgen production is stimulated.⁴ Estrogen then rises above normal, whereas the androgen remains normal.

The rudimentary ducts of the male breast are sensitive to increased estrogen levels,^{2, 10} and respond with hyperplasia of the ducts and the periductal connective tissue, resulting in true gynecomastia. In this series true gynecomastia appeared in 6 per cent to a mild degree, and in 4 per cent to an advanced degree, following receipt of Red Cross parcels subsequent to two years of starvation. Gynecomastia appeared in nearly 50 per cent of the prisoners after liberation and adequate diet, subsequent to 40 months of starvation.

Gynecomastia slowly disappeared, both during further starvation (average four months) due to diminished production of estrogen, and after adequate diet (average six months) due to recovery of the impaired liver and its subsequent inactivation of the excess estrogen.

A question naturally arises at this point: Why was there no gynecomastia seen in early starvation? Trentin and Turner¹¹ have shown that as the food intake level decreases, the amount of estrogen required to produce minimum duct growth responses of the mammary glands of male albino mice is considerable, and proportionately increased. Astwood et al.¹² have shown that the mammary duct system is much less sensitive to estrogen during inanition.

Hertz¹³ has reported that estrogen was less potent in the presence of a folic acid deficiency diet.

It would be interesting to be able to determine just which factors in starvation produced the diminished gonadotrophic, androgenic and estrogenic functions. The diet during starvation in the reported group was deficient in every type of food, vitamin, mineral, and often water. It was especially deficient in fat and protein. When the diet became adequate again, it was adequate in all respects. It is difficult, therefore, to lay the blame on any one specific element.

The chemical formulae of androgen and estrogen¹⁴ show them to be very similar steroids. To determine the source of these steroids, it is natural to investigate the steroids in the diet. There are at least two essential steroids in the normal diet: cholesterol and ergosterol. Although proof is lacking at this time, it is believed that the almost complete absence of these two steroids in the diet furnished by the Japanese may have played an important part in diminishing the estrogenic and androgenic functions, and that the subsequent supply of these steroids may have resulted in the stimulation of the androgenic and estrogenic functions.

SUMMARY

The normal liver inactivates excess androgens and estrogens, resulting in normal levels, and in a normal estrogen/androgen ratio. Severe starvation, directly as well as indirectly, inhibits the gonads, causing decreased androgenic and estrogenic functions and levels. An adequate diet for several weeks to months following severe starvation directly and indirectly stimulates the gonads to increased androgenic and estrogenic functions, with a return to normal levels. As long as starvation continues, the estrogen level does not go above normal due to diminished estrogen production; but when after starvation the diet is returned to normal, the liver, impaired by protracted starvation, becomes unable to inactivate any excess of estrogen that may be produced, resulting in an increased estrogen level and a reversal of the estrogen/androgen ratio. The rudimentary ducts of the male breast are sensitive to increased estrogen levels, and respond with hyperplasia of the ducts, and the periductal connective tissue (true gynecomastia).

True gynecomastia appeared to a mild degree in 6 per cent of the prisoners and to a severe degree in 4 per cent (total 10 per cent), following adequate diet (Red Cross parcels) subsequent to two years of starvation; and in nearly 50 per cent of the prisoners after liberation subsequent to 40 months of starvation. Gynecomastia disappeared both during further starvation (average four months) due to diminished function of the sex hormones, and after an adequate diet (average six months) when the liver recovered from its impairment and inactivated the excess estrogens. No malignancies were seen in this series during 22 months of observation.

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AMEBIC LIVER ABSCESS *

By MORRIS ZUCKERBROD, Major, M.C., AUS, JOSEPH LITWINS, F.A.C.P., Lt. Col., M.C., AUS, *New York, N. Y.*, FRANCIS T. ROGLIANO, Major, M.C., AUS, and DAVID JELLINGER, Lt. Col., M.C., AUS

AMEBIC abscess of the liver is the most important complication of amebiasis. It is not a rare condition. Its highest incidence is in the tropics and subtropics, but, while it is reputed to be rare in the temperate climates, there is evidence from autopsy records (Craig¹) that it is also fairly common in the temperate zones, though often not recognized during life. With the return of so many soldiers and civilians from areas in which amebiasis is endemic and epidemic, amebic abscess of the liver and amebic hepatitis will be seen much more frequently in the temperate climates. The following three cases occurring in a Station Hospital in New York within a relatively short time of each other demonstrate the need for entertaining the possibility of amebic liver involvement in the differential diagnosis of obscure cases of right upper quadrant pain, pleurisy with effusion, and sub-phrenic abscess.

CASE REPORTS

Case 1. History: A 38 year old sergeant was admitted to the hospital on December 3, 1945 with the following history. He was well until three days prior to admission when he developed pain in the right lower chest. This pain was aggravated by breathing and by lying on his right side. For the three days prior to admission he had been sleeping very poorly and the pain had become so severe the night prior to admission that he sat upright in bed the entire night. With the pain he had noticed the development of a slight hacking cough productive of small amounts of a whitish mucoid sputum. He had perspired profusely during the three days and felt very weak, but had not experienced any chills or fever. During the day prior to admission he had noted the development of edema of the feet.

Past History: In 1941, in the course of a routine physical examination, the patient was told that he had an enlarged liver but he was never hospitalized for this nor had he ever had any symptoms referable to his liver. He returned from the China-Burma-India theater of operations in October 1945 after having spent 26 months there. During this time he had lost about 30 pounds in weight. His diet had been inadequate because of combat conditions and for months on end consisted almost entirely of carbohydrate foods. He had always been a moderate drinker and had never imbibed to the point of inebriety. Since being home, he had eaten well of a balanced diet and had regained three or four pounds in weight. To his knowledge, he had never suffered from any frank avitaminoses during his stay in the CBI theater. He had, however, had four or five attacks of dysentery, all of which were treated with sulfaguandine with good response, and these attacks of diarrhea had never lasted more than two or three days and had never been bloody or profuse. The last attack of diarrhea occurred in August 1945 and a stool specimen examination at that time was supposed to have been negative for amebae. He regarded four or five loose bowel movements per day to be his normal bowel habit during the past two years.

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Family History: His mother and sister were both said to have had liver disease, but he could not elaborate on its exact nature. To his knowledge, no one in his family had ever had amebic dysentery or amebiasis.

Physical Examination: On admission the patient was orthopneic and dyspneic and acutely ill. Temperature 102.8° F., pulse 120, respirations 26, blood pressure 108 mm. Hg systolic and 70 mm. diastolic. He was not jaundiced, but he was obviously anemic. There were signs of weight loss. The right chest was splinted and there were dullness, diminished breath sounds, diminished fremitus, and a loud friction rub over the right lower chest. A few râles could be heard at both bases during inspiration and expiration. The abdomen was distended with gas and fluid and the liver edge could be felt about 4 cm. below the right costal margin, and the splenic edge about 2 cm. below the left costal margin. The umbilicus was protuberant and there were dilated veins over the lateral aspects of the abdomen and chest. The right upper quadrant of the abdomen was rigid and there was marked tenderness to palpation and percussion at the costal margin and the anterior axillary line on the right side. Examination of the heart was essentially negative. There was no venous distention in the neck or extremities but there was pitting edema of the feet. There was no edema over the sacrum or pre-tibially. Neurologic examination was entirely normal.

The blood count on admission revealed a red blood cell count of 3.2 million, with a hemoglobin of 8 grams. The red blood cells appeared normal. The white blood cell count was 29,500, polymorphonuclear leukocytes 80 per cent, lymphocytes 10 per cent and stab forms 10 per cent. Urinalysis was negative except for a trace of albumin. Serum proteins were 6.56 gm., albumin 3.75 gm., globulin 2.81 gm., and the albumin-globulin ratio 1.3. The icterus index was 3.5 units, and the thymol flocculation 5.0 units. The blood Kahn test was negative. Stool examination revealed no amebae, ova or parasites.

Course: Because of the findings in the chest, the leukocytosis and fever, it was felt that the patient had a bacterial pneumonia though a lesion beneath the right diaphragm was suspected. Accordingly, he was started on penicillin despite the fact that the sputum showed only a rare pneumococcus. The initial stool examination was reported to be negative for amebae. Fluoroscopic examination, however, disclosed a high fixed diaphragm on the right side with no definite involvement of the lung fields. This was confirmed on roentgenogram. During the course of the first 36 hours, the patient made no response to the penicillin which was given in adequate dosage (30,000 units q. 3 h) intramuscularly. Because the roentgen examination of the chest made one suspect a lesion beneath the right dome of the diaphragm, it was decided to sigmoidoscope the patient despite his critical condition. The sigmoidoscope was inserted only a distance of three inches and the rectal mucosa was observed to be markedly edematous and inflamed. A bloody, stringy mucus was seen to be literally pouring down from the rectum above, but no ulcers were visualized. Some of this material was suspended in warm saline and sent for laboratory examination. Because the patient was so uncomfortable, further manipulation was discontinued. The material obtained on proctoscopic examination contained numerous motile trophozoites of *Endameba histolytica*.

The patient was immediately started on 65 mg. of emetine hydrochloride intramuscularly daily and within 24 hours his temperature began to come down by lysis. Daily rises in temperature to 101° to 102° F. continued for seven days after the emetine was started. Because of the persistence of the low grade fever, the marked tenderness over the lower ribs, and the leukocytosis, it seemed probable that abscess formation had already occurred. Accordingly, on the seventh day after the emetine was started, liver aspiration was performed and 450 c.c. of anchovy paste material removed. Laboratory examination of the abscess contents revealed cellular debris; no amebae were seen. Two hundred c.c. of air were injected and roentgen studies



FIG. 1a (above). *Case 1.* Elevation of right leaf of diaphragm which was immobile on fluoroscopy.

b (below). *Case 1.* Fluid level in cavity in liver after aspiration and injection of air. Pleural reaction is also seen.

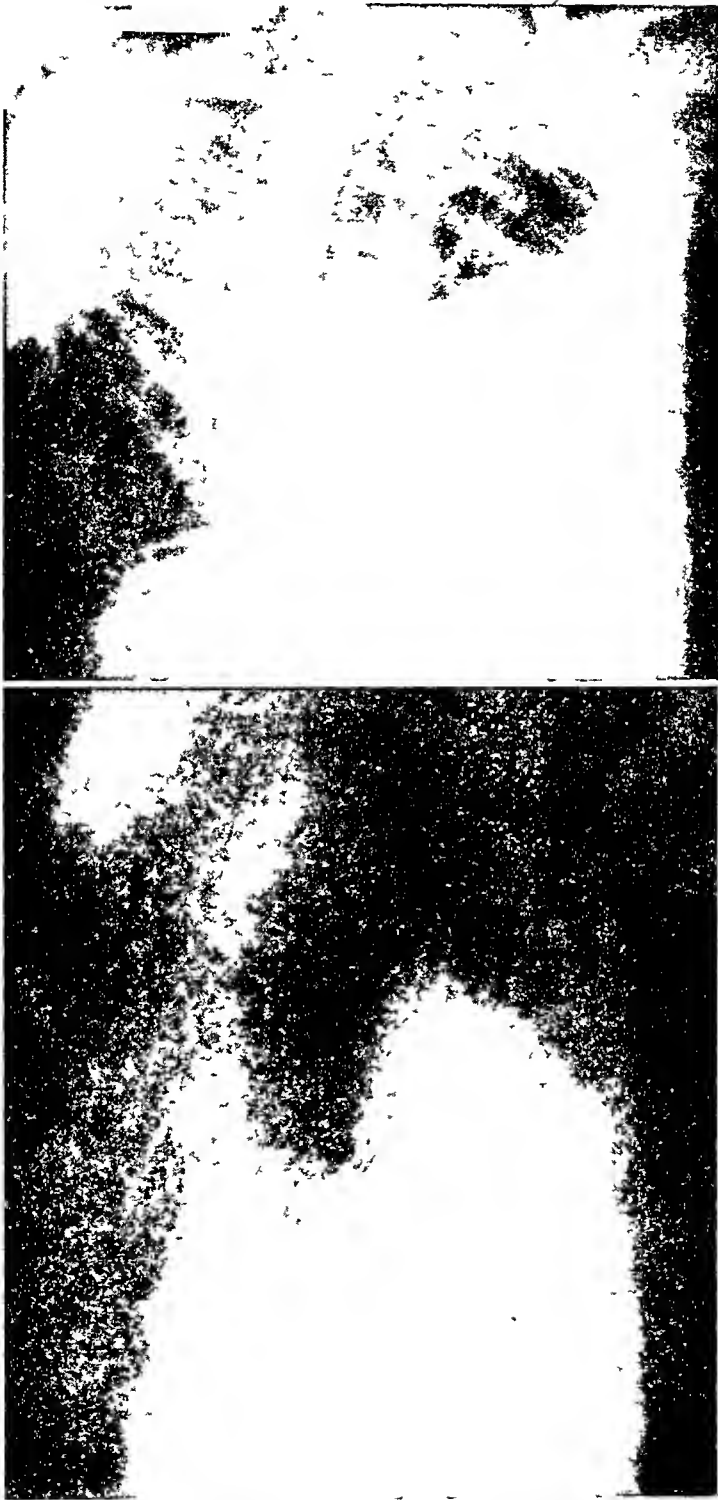


FIG. 2a (above) *Case 1* Oblique view shows increased elevation of diaphragm with small bubble of air remaining in cavity

b (below) *Case 1* Film taken after lipiodol injection into right lung showing communication between right middle lobe bronchus and cavity in liver. Some of the lipiodol is seen at the bottom of the liver cavity and a small amount is seen floating on the surface of the fluid.

done immediately afterwards demonstrated a large cavity in the right lobe of the liver beneath the diaphragm.

The edema of the feet and the ascites, which the patient had on admission, were difficult to explain at first. The serum proteins were low but greater than the so-called critical level, and the albumin-globulin ratio was not reversed at this time. Heart failure was not present inasmuch as the heart size was normal and there was no venous distention, and the edema was not dependent. The only electrocardiographic abnormality consisted of low amplitude QRS complexes in the limb leads. The possibility of an avitaminosis was strong in view of the long history of malnutrition, and accordingly the patient was put on bed rest and given thiamine chloride and liver extract intramuscularly and multivitamin capsules by mouth. At the end of 12 days, the edema of the feet had entirely disappeared and the ascites had definitely decreased. It was only at this time that reversal of the albumin-globulin ratio was demonstrated. (Total protein 6.85 gm., albumin 2.75 gm., globulin 4.10 gm., albumin-globulin ratio 0.60.)

It is interesting to note that during the course of the acute illness the patient had no jaundice and the thymol flocculation test was normal. The only abnormality in blood chemistry was found in the total cholesterol, which was at the lower level of normal (total cholesterol 120 mg., free cholesterol 32.5, ester 87.5, ratio free: total—0.27). Fluid intake and output never showed any great disparity; there was no change in blood pressure, and serial electrocardiograms showed no change during the course of emetine administration.

In the course of the next five weeks, the patient made slow but steady progress. To combat the anemia, the patient was given one transfusion of 500 c.c. of compatible whole blood, liver extract intramuscularly and ferrous sulfate by mouth. By December 27, 1945 his red blood cell count had climbed to 4.65 million, and the hemoglobin to 13.5 gm. A leukocytosis of 12 to 20 thousand persisted. The liver became smaller, and the spleen could no longer be felt. Tenderness of the liver to percussion and palpation decreased. Aspiration of the abscess was performed seven times, and the total amount removed was 2725 c.c. The aspirated material was always of anchovy paste color and consistency, always sterile, and never were amebae found. The size of the liver abscess cavity did not decrease appreciably despite the removal of this large volume of pus. Râles in the right base, along with dullness to percussion, diminished tactile fremitus and breath sounds persisted. The right diaphragm remained at a high level. There were occasional small rises in temperature. However, the pulse rate was always disproportionately rapid.

It seemed that operative intervention would be necessary ultimately because of the inability to drain the abscess cavity completely. However, because of the improvement of his general condition with the use of emetine and diodoquin, it was decided to give him two courses of these medications before open operation was attempted.

On January 8, 1946, a day after the second course of emetine had been completed, chest aspiration was attempted because the patient had begun to run fever and have some increase in chest pain, though there were no changes in the physical examination or the roentgenogram. Despite the fact that the needle was inserted in six or seven sites, only 75 c.c. of pus were obtained. Thereafter, the patient's temperature kept rising to a progressively higher level, he became more anemic, and chest pain became more pronounced. A second course of diodoquin and penicillin was started. During the course of the next week no improvement was apparent. On January 15 he developed a severe cough and began to expectorate large amounts of bloody sputum. On examination the sputum failed to reveal any amebae.

At this time, there was no change in either physical examination or roentgen findings. It was felt that the liver abscess had probably ruptured through the diaphragm into the lung, despite the fact that there was no film or fluoroscopic evidence of involvement of the lung parenchyma (case 1, figure 2a).

On January 17, 1946, thoracotomy was performed, and about 2000 c.c. of a mixture of blood and pus were evacuated from the liver. A drainage tube was left in situ. For a week the post-operative course was stormy, and the patient continued to run fever, and to cough and bring up bloody sputum. He was given supportive treatment—transfusions, liver extract, and a high protein diet. While the pus at operation was shown to be sterile, the sputum contained a hemolytic streptococcus. Accordingly, the penicillin was continued at 30,000 units every three hours. There was practically no drainage from the tube inserted at operation.

On January 26, 1946, the temperature reached a normal level, and has remained there since. On January 28, the drainage tube was removed and the penicillin discontinued. Roentgenogram of the chest on January 31 showed the right diaphragm at a lower level, and a definite diminution in the size of the subdiaphragmatic bulge.

The patient continued to have a severe cough and to expectorate large amounts of bloody sputum. Repeated examination of the sputum and stools failed to reveal trophozoites or cysts of *E. histolytica*. Despite these negative laboratory findings, a third course of emetine hydrochloride and diodoquin was given. On February 20, 1946, bronchoscopy and lipiodol instillation were performed, and roentgen examination immediately thereafter revealed a communication between the right middle lobe of the lung and a multilocular cavity in the right lobe of the liver (case 1, figure 2b).

At the time of this report, the patient seems to be making a satisfactory recovery. Several days after the lipiodol instillation, the expectoration ceased, and the cough has become much less aggravating. The last roentgen report on March 4, 1946 showed diminution in the amount of lipiodol in the right lung and liver abscess and some decrease in the size of the liver abscess. The patient recovered clinically and roentgenologically within several weeks.

Case 2. Chief Complaint: A 27 year old Negro private was admitted to the Fort Jay Station Hospital on November 13, 1945. The chief complaint was pain in the right lower chest since October 26, 1945.

Present Illness: On October 26, 1945, some three days prior to boarding ship for return to the United States, the patient had a shaking chill and pain in the right upper abdomen. These symptoms lasted but a few hours and he felt well until five days later when he had a recurrence of the right abdominal pain. Associated with this was right lower chest pain aggravated by respiration, and fever. He was admitted to the ship's sick bay on October 30 and there a diagnosis of pleurisy with effusion was made but no chest aspiration was performed. He had a low grade fever, a leukocytosis of 16,000 and a roentgenogram showed that the right lower chest was radio-opaque. He was transferred to Fort Jay on November 13 for further study.

Past History: The patient stated that he had always been a very moderate drinker, consuming at most two or three glasses of beer several nights a week. Since January 1943, exclusive of the present admission, the patient had been hospitalized five times for "right-sided pleurisy." The last hospitalization, prior to the present one, occurred in August 1945 at which time, following exposure to inclement weather, he developed a temperature of 103°, pain in the right lower chest, and a non-productive cough. The fever persisted for two weeks and then disappeared. He was hospitalized for a total period of six weeks and he was kept in bed for four weeks. At the time of discharge to full duty, a roentgenogram of the chest was said to be normal and the patient was told he had a pleurisy without any fluid. From that time until his present illness, he had been able to perform all duties and felt perfectly well. However, during that illness he had lost about 12 pounds in weight and has since been unable to regain them. The remainder of his past history and family history were non-contributory, except for the fact that he had spent his entire life, prior to army service, in Louisiana. Overseas, he had served in the European Theatre of Operations.

Physical Examination: At the time of admission, the patient appeared chronically ill but in no acute distress. The only significant findings were in the right lower chest

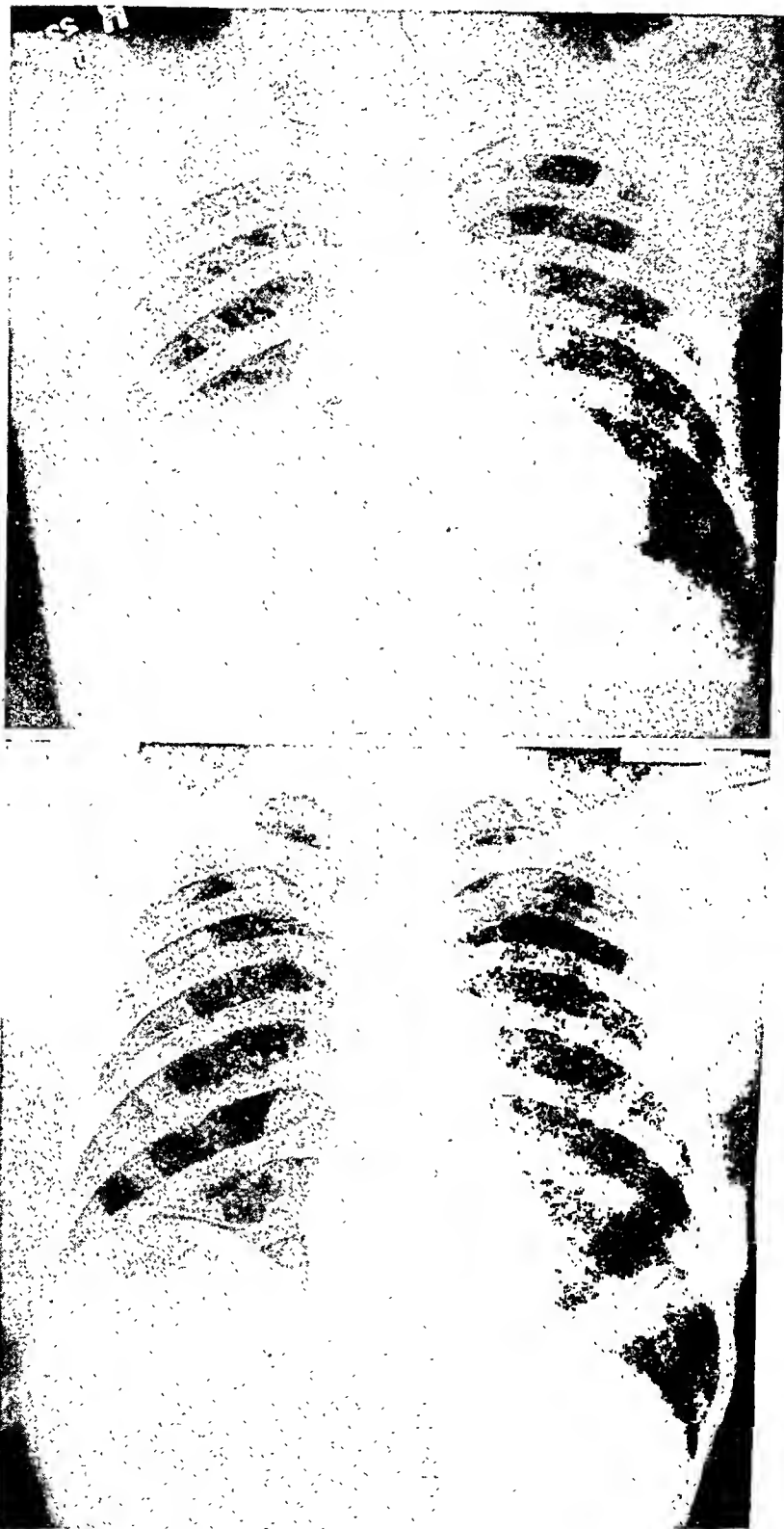


FIG. 3a (above). Case 2. Elevation of right diaphragm.

b (below). Case 2. After aspiration and injection of air shows fluid level in cavity below diaphragm.

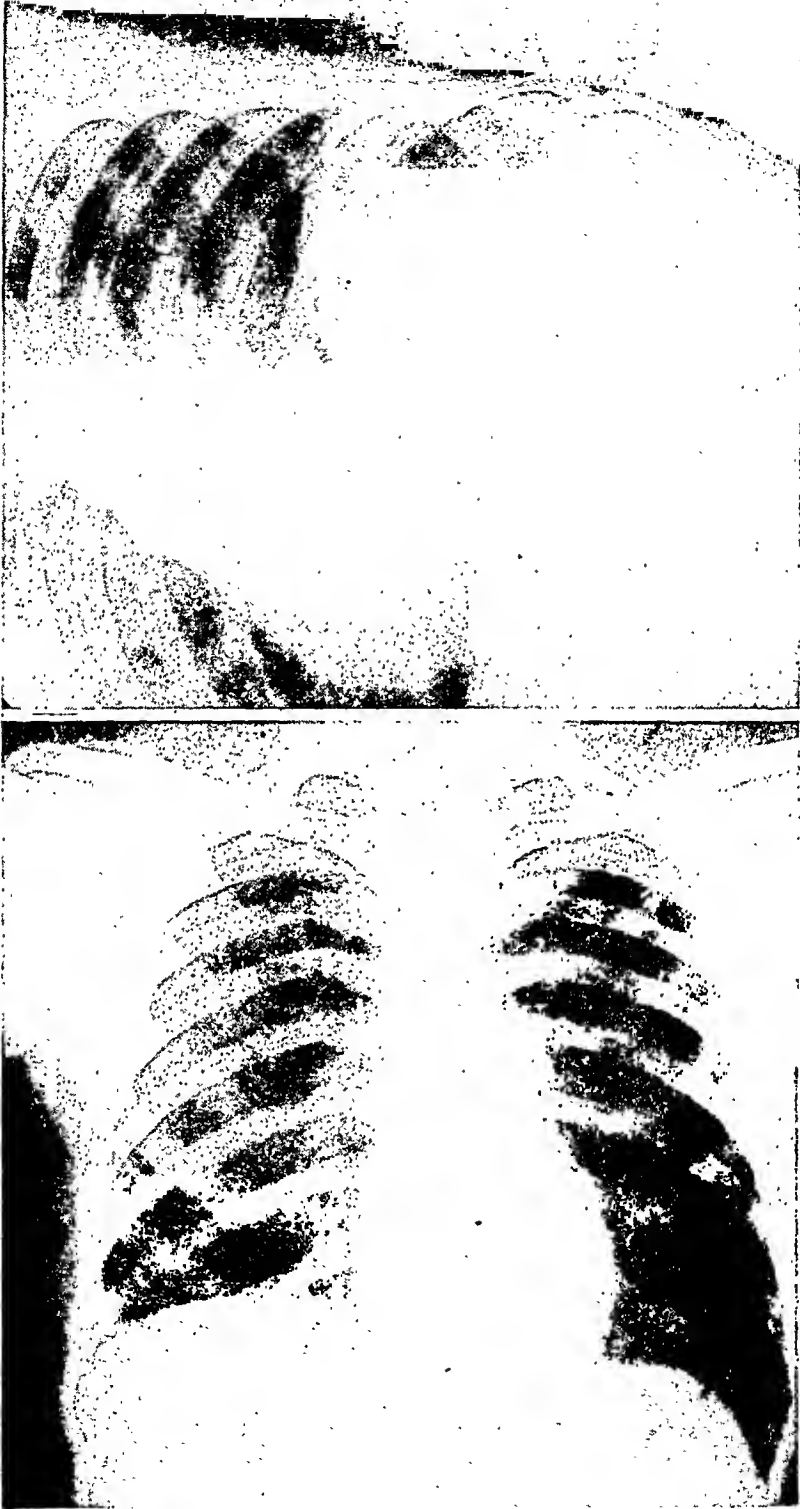


FIG. 4a (above). *Case 2.* Left decubitus film taken on November 29, 1945 shows shifting fluid level and large size of cavity.

b (below). *Case 2.* Film taken on January 3, 1946 (five weeks later) shows slight amount of residual air in cavity and much less elevation of diaphragm.

and in the right upper quadrant of the abdomen. The lower half of the right chest was dull to percussion and there were markedly suppressed breath sounds and decreased tactile fremitus. No râles were heard. There was tenderness to pressure over the right upper anterior abdomen and there was tenderness to fist percussion along the right costal margin. There was no spasm or rigidity, and no organ edges or masses could be felt. There was no shift of the trachea and there was no jaundice.

Course: On admission, the blood count was normal, the total white count being 9650, 70 per cent polys, 28 per cent lymphocytes, and 2 per cent monocytes. The urine was completely negative and the stool was negative for amebae and other parasites. The patient had a low-grade fever. Two days after admission a diagnostic paracentesis was performed and 20 c.c. of a thick, bloody, purulent fluid were removed. This contained many pus cells. There were no recognizable tissue cells aside from this and no acid-fast organisms were observed. During the next 10 days the patient ran a low grade fever and his white count rose to 14,000. Three stool specimens were negative for amebae and sigmoidoscopy was entirely negative. It was felt that the patient probably had an amebic liver abscess and on November 26 he was fluoroscoped prior to doing another paracentesis. Fluoroscopy revealed a smooth high right diaphragm which barely moved on respiration, and this examination suggested that all the pathology was directly below the diaphragm (case 2, figure 3a). On November 29 a paracentesis was performed and 180 c.c. of anchovy paste material were removed. Sixty c.c. of air were injected into the cavity and roentgen studies done immediately thereafter showed a large abscess cavity within the right lobe of the liver just beneath the diaphragm (case 2, figures 3b and 4a). Accordingly, the patient was started on a course of emetine hydrochloride. On December 3, paracentesis was again performed in an attempt to empty the abscess cavity completely, and 70 c.c. of reddish-brown purulent material were removed. Emetine hydrochloride 65 mg. was injected into the cavity.

From the time the course of emetine was started until the present, the patient has made progressive improvement. His temperature has stayed at a normal level, the diaphragm has come down, and the chest and abdominal tenderness has disappeared. His blood count has become normal. On January 13, 1946, after the patient had received two courses of emetine and two courses of diodoquin, a roentgenogram revealed almost complete disappearance of the abscess cavity and a return of the right diaphragm to a normal position (case 3, figure 4b). Icterus index, blood protein, blood cholesterol, and thymol flocculation were always within normal limits.

On January 25, the patient was transferred to a Veteran's Administration Hospital for further observation. At that time physical examination was entirely normal, and the patient felt perfectly well.

Case 3. Chief Complaint: A 30 year old officer was admitted to the hospital on December 17, 1945 with the chief complaints of fever for 12 days and right lower chest pain for five days.

History of Present Illness: The patient claims he was well until about November 5, 1945 at which time he was on board ship on his way to the United States from the China-Burma-India theater. At that time he developed a "head cold" characterized by a running nose and a cough productive of small amounts of white mucoid sputum. He noticed also that he had lost his appetite. After several days these symptoms diminished considerably and he was not hospitalized. About a month later, while on terminal leave, he began to have pain in his right lower posterior chest and about three days later the pain began to get more severe and moved anteriorly so that it was now located in the region of the gall bladder. He noted that breathing and certain movements aggravated the pain. Since boarding ship he had lost about 15 pounds. Along with the aggravation of the pain, he had daily fever up to about 102° F. He was treated by a local physician for an inflamed gall-bladder for about 10 days and because he did not improve, he appeared at an army dispensary and was hospitalized.

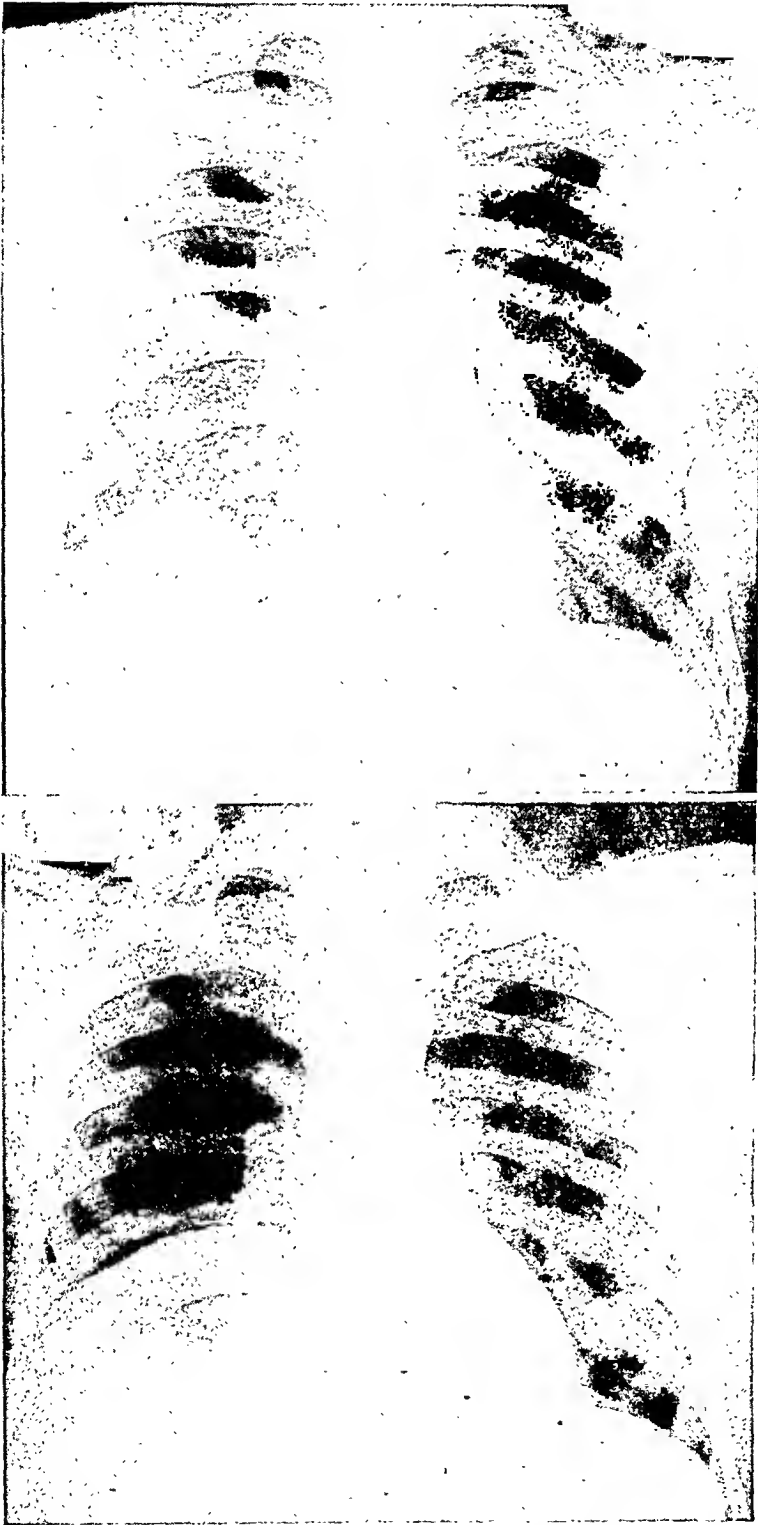


FIG. 5a (above). *Case 3.* Localized elevation of right diaphragm.

• *b* (below). *Case 3.* After aspiration and injection of air shows large amount of air in cavity below diaphragm. Also shows small amount of air in communicating cavity in liver.

Past History: He had always been in good health and never had diarrhea or dysentery. He had spent about 10½ months in the Pacific area. In May and June of 1945 he had dengue fever and jaundice from which he recovered in several weeks. He is a moderate consumer of alcohol and tobacco. Family history was not relevant.

Physical Examination: On admission the patient was acutely ill. Temperature 104° F., pulse 140, respirations 26, blood pressure 130 mm. Hg systolic and 78 mm. diastolic. Physical examination was entirely negative except for dullness on percussion, diminished breath sounds and tactile fremitus in the lower right chest and limitation of movement of the diaphragm on the right side. There was tenderness to fist percussion all along the right costal border. The liver edge could be felt on deep inspiration and was tender. There was no jaundice and the patient was obviously anemic. The spleen could not be felt. There were no dilated veins over the abdomen. The remainder of the physical examination was entirely normal.

Course and Laboratory Work: On admission a roentgenogram of the chest revealed an elevated right diaphragm which was fixed on fluoroscopy (case 3, figure 5a). Urine examination was entirely negative. The blood examinations showed: red blood cells 3.66 million; hemoglobin 12.5 gm.; white blood cells 8,750, polymorphonuclears 59 per cent, lymphocytes 40 per cent, monocytes 1 per cent. The icterus index was 6 units. During the next six days, the patient ran a septic course with a daily temperature of 104°, and it was felt that the patient had a sub-diaphragmatic abscess. His white count rose to 15,000, with 81 per cent polymorphonuclears, and he became more anemic. Repeated stool examinations were negative for amebae and other parasites.

On December 19, 1945, a roentgenogram showed a sharply circumscribed elevation of the posterior portion of the right diaphragm. The patient was put on penicillin units 30,000 every four hours and sulfadiazine so that the blood level was 21 mg. per cent, without improvement. On December 25 the patient had a severe coughing spell at the conclusion of which he raised several ounces of a colored sputum mixed with blood which on examination failed to show any amebae. Because his course was such that amebic liver abscess was a probable diagnosis, and because of the probability that the episode of coughing and hemoptysis was the result of the rupture of the liver abscess into the lung, a diagnostic paracentesis was performed between the eighth and ninth ribs in the posterior axillary line and 350 c.c. of cream-colored pus were removed. This material had no odor and on examination revealed only many streptococci and pneumococci but no amebae. A roentgenogram done immediately after the paracentesis showed a multilocular abscess cavity beneath the right diaphragm with a fluid level (case 3, figures 5b, 6a).

Because the pus was not characteristic of amebic liver abscess and contained streptococci and pneumococci, and two sigmoidoscopic examinations and repeated stool examinations failed to demonstrate either a colitis or amebae, the patient was continued with penicillin and sulfadiazine for further trial. He was transfused twice. Despite this, the fever and leukocytosis continued and by December 31, 1945 it was felt that adequate trial with the penicillin and sulfadiazine had been given. Accordingly, he was started on emetine hydrochloride 65 mg. intramuscularly every day. There was dramatic improvement. The cough stopped, the pain vanished, and on January 4, his temperature became normal and it has remained normal until the time of this report. On January 5, paracentesis was attempted and only 30 c.c. of a thick, yellow-brown pus were obtained. Roentgen examination at this time demonstrated no change. The patient continued to improve and emetine hydrochloride was discontinued on January 9. On January 10 he was started on a course of diodoquin. At this time his blood count was entirely normal, red blood cells 5.1 million, hemoglobin 15 gm., white blood cells 8,000. On January 14 roentgenograms showed complete disappearance of the cavity and the right diaphragm was only slightly elevated posteriorly. Another course of emetine hydrochloride, 65 mg. intramuscularly daily, was started on January 29 and was continued for 10 days. On February 1, repeat roentgenograms showed



FIG 6a (above). *Case 3* Left decubitus film showing that cavity is multilocular with at least two distinct shifting fluid levels

b (below) *Case 3* Five weeks later, showing essentially normal appearing diaphragm.

no evidence of cavity. The only residual was a slightly elevated diaphragm posteriorly. At the time of writing the patient feels perfectly well, has regained most of the weight he lost, has an excellent appetite. There is no tenderness on percussion over the liver. Roentgen studies on February 14 (case 3, figure 6b) showed complete disappearance of the previously described elevation of the right diaphragm.

COMMENTARY

The frequency of occurrence of amebic liver abscess varies so widely in the reports in the literature that an accurate statement is not possible.^{2, 3, 4, 5} Perhaps overall 8 per cent or 9 per cent of cases of amebiasis with clinical symptoms develop liver abscess. Usually the right lobe of the liver near the dome of the diaphragm is involved, and most commonly the abscess is single. Multiple amebic liver abscesses are not as rare as once supposed. They usually are found in severe cases that come to autopsy. Cases of amebic liver abscess that can be effectively treated by repeated aspiration or surgery are usually single. The relation of amebic liver abscess to intestinal amebiasis, dysentery and colitis is so irregular that the failure to find amebae in the stool or an active colitis is of no value in excluding the disease.

In the three cases presented, amebae were found in the stools only in case 1, despite the fact that in all three cases some of the mucus from the bowel wall was suspended in warm saline in the course of a sigmoidoscopy. Not once was a routine stool examination positive.

Of the complications of amebic liver abscess, rupture into the pleura or lung is by far the most common.⁶ Craig⁷ tabulated 624 cases of amebic liver abscess, in which rupture had occurred in 192 (30 per cent). Of this number, 70 (36 per cent) ruptured into the pleura, and 47 (24 per cent) into the right lung. These instances of rupture usually occur in large liver abscesses of long standing situated beneath the dome of the right diaphragm. While the occurrence of pulmonary involvement is usually manifested by the expectoration of a bloody or brownish sputum, the insidious onset of cough, chest pain, small amounts of white mucoid sputum, and presence of bubbling râles may antedate the frank lung abscess formation or hemoptysis by many weeks.

In the three cases presented, the clinical course was such that it was felt that rupture of the liver abscess into the lung had occurred in cases 1 and 3. In neither of these was there any frank roentgen evidence of involvement of the lung parenchyma. In neither case were amebae demonstrated in the sputum. However, neither could they be found in the material aspirated from the liver abscesses. In case 3 there was dramatic cessation of the cough and expectoration following the exhibition of emetine. In case 1 the lung involvement was of long duration and was probably complicated by secondary infection.

The laboratory studies in the three cases were of interest because the liver function tests, icterus index, serum proteins and cholesterol, thymol flocculation, were abnormal only in case 1, and here the abnormality was mani-

fested by a reversal of the albumin-globulin ratio (albumin 2.75 gm., globulin 4.10 gm., A/G ratio 0.60) and a total cholesterol value at the lower limit of normal (120 mg. per cent). One cannot ascribe too much significance to these findings because of the long history of inadequate diet. The thymol flocculations were within normal limits, being five units or less. There was moderate leukocytosis (14,000 to 16,000) in cases 2 and 3 and marked leukocytosis (30,000) in case 1. This figure was indicative of secondary infection, though such high counts occur in amebic hepatitis prior to abscess formation. In cases 1 and 3 there was a severe anemia of normocytic, normochromic variety which disappeared when the infection was controlled.

The value of roentgen and fluoroscopic examination in the diagnosis of liver abscess is well known. When the patient is first seen, fluoroscopic examination is necessary to determine whether the lesion is above or below the diaphragm and whether it is located anteriorly or posteriorly. During fluoroscopy the skin can be marked, indicating the optimum site for paracentesis, after which air is injected. Shaking the patient during fluoroscopy may cause splashing of the abscess contents and demonstrate that the contents are freely movable.

Radiographic examination in various positions before and after paracentesis, followed by injection of air, is probably the most important procedure in establishing a diagnosis of liver abscess, and demonstrating its size. Films taken in the antero-posterior, lateral, and decubitus positions will show shifting of the fluid level and will enable measurement of the cavity in three planes, giving an approximation of its size.

Films repeated at intervals during therapy will demonstrate the effect of therapy and improvement will be indicated by a diminution in the size of the cavity.

The treatment of amebic liver abscess depends primarily upon the administration of emetine hydrochloride subcutaneously—65 mg. daily for a period of eight to 10 days. Such a series of injections is commonly called a "course of emetine." The general opinion among authorities is that intestinal amebiasis exists in almost all cases of amebic liver abscess for a longer or shorter period of time prior to the development of liver infection. Because emetine alone cannot be relied upon to cure intestinal amebiasis,¹¹ it is necessary to follow the course of emetine with one of the amebicidal iodine compounds (diodoquin, chiniofon, vioform) by mouth. We used diodoquin (0.6 gm. thrice daily for 10 days) because of its effectiveness and lack of toxicity. Carbarsone was not used because of the possible hepatotoxic effects.

There is divergence of opinion as to whether or not aspiration should be performed routinely. The preponderant evidence seems to be in favor of a combination of emetine, diodoquin and aspiration as yielding the best results, though there is evidence to the effect that even large abscesses may be cured by emetine alone.^{8, 9, 10}

Aspiration should not be done before the end of the first week of emetine administration unless there is a question of diagnosis or if rupture appears imminent. The reason advanced is that the liver, in the stage before the emetine has exerted a therapeutic effect, is usually large and engorged, and the danger of hemorrhage incident to needling is great.

How many courses of emetine can be regarded as adequate therapy for liver abscess cannot be stated with certainty. One course of therapy usually brings about rapid improvement, and if, at the end of such course, improvement is not evident or is not as complete as expected, secondary infection may be present. In our three cases there was marked improvement in all at the end of the first course of treatment, though in case 1 a leukocytosis and occasional low grade temperature elevation were still evident. In cases 2 and 3, the blood counts and temperature were normal. Nevertheless, a second course of emetine was given three weeks after the first in case 1 because of the persistent reaccumulation of fluid, in case 2 because there was little apparent roentgenographic improvement, and in case 3 because of the small area of subdiaphragmatic involvement which, while unattended by clinical findings, was persistent in roentgen studies. At the end of the second course of treatment, cases 1 and 2 were unchanged, but case 3 had improved so markedly that the last roentgenograms showed a normal right diaphragm and a tiny residual cavity at the site of the previous large one. In case 1, a third course of emetine and diodoquin were given because of the persistent cough and bloody expectoration and it was only at the completion of this third course of treatment that the amebic infection was controlled satisfactorily. We feel that only long observation will be able to tell the whole story.

Emetine is a potent protoplasmic poison with a cumulative effect and a small margin of safety. Consequently toxic effects must be guarded against very carefully. The two most important signs of toxicity are myocardial damage and peripheral neuritis. The myocardial involvement is manifested by a fall in blood pressure and/or the appearance of an arrhythmia. Therefore, before emetine is administered, the blood pressure should be taken and an electrocardiogram made. Thereafter, during the course of treatment, the blood pressure should be recorded twice daily, and an electrocardiogram made at least every other day. Emetine should be discontinued immediately upon the appearance of an electrocardiographic abnormality or a significant fall in blood pressure. Even if the drug is tolerated, it should not be repeated sooner than three or four weeks after the end of the previous course.

We observed no toxic reactions from the emetine in our cases. In case 1, the initial electrocardiogram showed low voltage QRS complexes, but this was not regarded as a contraindication to the administration of emetine because it was felt that this electrocardiographic abnormality was the result of his severe infection and state of malnutrition. No electrocardiographic changes were observed during the course of emetine administration either in case 1 or the other two cases, nor were there any changes in the blood pressure levels.

The consensus of opinion with regard to open operation is that adequate trial with emetine and aspiration should always be made before such intervention is attempted unless an emergency exists.^{8,9} This is true even if perforation into the adjoining viscus occurs. Open operation is attended by much higher mortality than the more conservative methods, though of course the severity of the disease in cases that come to open operation must be taken into account. Open operation should be considered when (1) fever and leukocytosis persist and the secondary infection cannot be controlled by the sulfonamides or penicillin; (2) when involvement of other organs demands it.

Case 1 came to operation because of the persistent fever and the inability to control the secondary infection. Case 3, despite the rupture into the lung, has done so well on emetine and aspiration that it appears probable open operation will not be necessary. (This patient was finally discharged as cured, without surgery.)

SUMMARY

1. Three cases of amebic liver abscess with roentgen and clinical findings are hereby presented.

2. The necessity for entertaining this diagnosis in cases of right upper quadrant and right lower chest pain associated with a high right diaphragm is stressed.

3. Injection of air followed by roentgen study is suggested in the course of diagnostic and therapeutic paracentesis.

4. While the finding of amebae in stools on routine examination or on sigmoidoscopy is helpful in making the diagnosis of amebic liver abscess, even repeatedly negative stool examination should not exclude this diagnosis.

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STUDIES WITH MEDICATED AEROSOLS

THE USE OF THE LUNGS AS A PORTAL FOR THE INTRODUCTION OF THERAPEUTIC AGENTS FOR SYSTEMIC EFFECT * †

By SAMUEL J. PRIGAL, ‡ M.D., *New York, N. Y.*

EVIDENCE presented below indicates that the lungs, because of their anatomic structure, can serve as an excellent means for the introduction of certain medications, in aerosol form, § intended for systemic action. Aerosol therapy differs from inhalational therapy in which gases have been employed in the treatment of cardiorespiratory diseases. Gas therapy is now an established procedure (Barach,¹ Segal,²) and is beyond the scope of this paper.

In recent years, medicated aerosol therapy has been advocated for the treatment of pulmonary diseases. Thus, for asthma, epinephrin aerosol has been used either by hand bulb nebulizer,³ or by the continuous inhalation method using oxygen as a driving force.⁴ For lung infections, aerosols of sulfathiazole have been introduced^{5, 6}; and as penicillin was investigated in the treatment of infection, it was logical to adopt the aerosol method in the treatment of infections involving the lung.⁷ Streptomycin is now similarly employed.⁸ It has become evident from studies with penicillin aerosol that this drug can be introduced for systemic action via the lungs.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

Embryologically, the lungs are an outgrowth of the gastrointestinal tract whose functions are ingestion, absorption, and secretion (in addition to digestion), precisely the functions of the lungs. Another function common to both organs is peristalsis. It is little known and appreciated that the lung has peristaltic action⁹ capable of inducing "tracheal vomiting."¹⁰ The stomach and intestines deal primarily with solids and liquids; the lungs with gases, and possibly liquids under certain conditions. Thus, recent evidence by Davis and Potter¹¹ indicates that during the intrauterine period the human fetus respire by active circulation of amniotic fluid throughout the lung fields. It is only at birth that air is substituted for the amniotic fluid.

Anatomically, the structure of the lung is ideal for the function of absorption. Repeated branching of the bronchi and bronchioles into the terminal air sacs provides the lungs with an estimated 300,000,000 alveoli, whose walls are essentially composed of capillaries having membranes

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‡ Chief, Allergy Clinic, New York Medical College-Flower-Fifth Avenue Hospital, New York City.

§ An aerosol or mist is a suspension of minute particles in air.

1/30,000 of an inch thick, the thinnest in the body. This provides about 700 sq. ft. of surface for absorption¹²—another remarkable instance of special structure for special function.

EVIDENCE OF ABSORPTION THROUGH THE LUNG

Clinical and experimental evidence shows that absorption of some substances in vapor, dust, or aerosol form occurs almost instantly. Thus, an allergic patient highly sensitive to fish may, on simple inhalation of the odor of fish, immediately develop hives. This would indicate that absorption and systemic circulation had occurred which permitted the allergen to reach the capillaries of the skin. Likewise, anaphylactic shock can be induced almost instantaneously in a sensitized guinea pig, on exposure to the specific allergen in dust form.^{13, 14} The rapidity of reaction is remarkable, and is an index of the rapidity of absorption through the lungs.

The absorption of an aerosol through the lungs depends upon the stability of the aerosol, the nature of the material aerosolized (whether protein or non-protein) and the type of solvent used.

If a stable aerosol is not produced, it does not reach the alveoli in sufficient quantity for absorption to take place. Aqueous solutions do not usually produce stable aerosols unless other chemicals such as glycerine, urea or potassium chloride are added.¹⁵ Oils are considerably more stable as aerosols. Propylene glycol, which is miscible with water in all proportions and which has a high viscosity, thereby resembling an oil, has been highly effective in the production of stable aerosols of penicillin, which it readily dissolves.¹⁶ According to Abramson,¹⁷ the formation and stability of a given aerosol depend upon the vapor pressure, the size of the droplets, density of material, and its surface tension.

As for the size of the aerosol particles in relation to its absorption, it has been indicated that particles of $2\ \mu$ or less readily reach the alveoli. Sizes above that are less likely to do that.¹⁷ It is possible, nevertheless, that larger particles are also absorbed, in view of the fact that large quantities of solutions may be absorbed when instilled into the lung of an anesthetized animal (as much as 20 c.c. per kilo, according to Winternitz and Smith.¹⁸) Large particles may, however, act as foreign bodies, initiating the cough reflex with expulsion of the droplets.

The nature of the material in aerosol form determines its absorbability. Aerosol of insulin, a complex protein, is absorbed slowly as was observed in recent experiments.¹⁹ Sodium sulfadiazine²⁰ and penicillin, less complex in chemical structure²¹ are quickly absorbed.¹⁶ The same holds true for the absorption of solutions instilled into the lungs of anesthetized animals. Winternitz and Smith¹⁸ showed that solutions of normal saline, or of phenolphthalein, rapidly pass the lung barrier. In sharp contrast, Fox²² using antibodies (in serum) observed very slow absorption—a finding which was confirmed by Drinker, Warren, and MacLanahan.²³ These workers instilled

horse serum, crystallized hemoglobin, and crystallized egg albumin into the lungs of dogs, and found delayed absorption of these proteins. Of these, the egg albumin was more readily absorbed, due probably to its smaller molecular size. By cannulating the thoracic duct, it was possible to demonstrate experimentally that the absorption of liquids from the lungs occurs through the capillary bed, and not through the lymphatic circulation.

Clinically, too, we have evidence of rapid absorption of fluids from the lung in the response to treatment of patients with pulmonary edema. Intravenous injections of hypertonic glucose, or the application of oxygen under positive pressure, may cause rapid and striking reversal of the edema by resorption.²⁴

Unlike fluids which are absorbed directly through the capillaries, particulate matter reaches the circulation indirectly through the lymphatic system (Drinker and Field²⁵).

Extreme caution must be observed in the introduction of certain substances into the lung. The toxic effect of some gases, such as mustard or chlorine, are well known. Strong acid, when instilled into the lung, produced pulmonary congestion resembling that of influenza (virus) pneumonitis.²⁶ Animal oils and fats, according to Pinkerton²⁷ when instilled into the lungs produced fibrosis, and mineral oil caused consolidation. Neutral vegetable oils, however, such as sesame and poppyseed, caused no reaction. Pinkerton observed, as well, that the absorption of oil from the lungs was exceedingly slow.

METHODS OF PRODUCING EFFECTIVE AEROSOLS FOR THERAPEUTIC PURPOSES

The simplest device available for producing aerosols is that of the nebulizer and rubber bulb. Squeezing the bulb generates the aerosol by the rapid passage of air through the nebulizer. Since the publication of Graeser and Rowe,³ this has become a popular method of treatment of asthma, utilizing epinephrin 1-100. Where the continuous production of an aerosol is desired, the hand bulb is replaced by an oxygen tank. This method was introduced by Richards, Barach, and Cromwell⁴ for the treatment of status asthmaticus, with a continuous flow of either epinephrin 1-100, neosynephrin, or other medications. Following Bryson's²⁸ successful production of an aerosol of penicillin capable of inhalation and absorption, Barach and his associates used the continuous method (oxygen and nebulizer) for the treatment of respiratory conditions with penicillin aerosol.⁷ The oxygen serves primarily as a driving force; in cases of anoxemia, the oxygen exerts a therapeutic effect as well.

Our own interest in aerosols followed the publications of Stacey⁵ and of Applebaum⁶ who successfully treated lung infections with an aerosol of sodium sulfathiazole, utilizing the oxygen-nebulizer method. This was prior to the introduction of penicillin for similar purposes. It was our purpose,

as well, to provide a cheaper source of power than oxygen, and attention was focused on steam. After a search, an apparatus originally designed for dispersion of insecticides was located, which is a combined steam-generator and aerosolizer.* It eliminated oxygen and the fragile nebulizer as well. This apparatus has been described in detail elsewhere.^{20, 29} To it has been added a valve which controls the onset and rate of flow of medication. This apparatus can aerosolize many solutions—sulfadiazine, penicillin, epinephrin, aminophyllin, insulin, ammonium chloride, and propylene glycol.²⁹

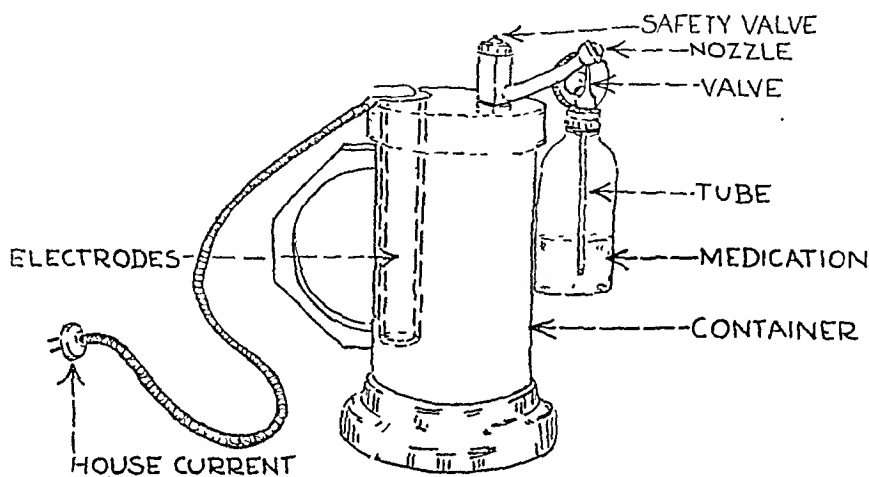


FIG. 1. A combined steam generator and aerosolizer.

Briefly, the apparatus consists of a container holding water (figure 1). Upon the application of electric current acting through electrodes suspended in the water, the latter is rapidly heated and converted to steam. The steam emerges from a spout which is specially designed to allow a thin trickle of the steam under pressure to pass over a tube with which it is connected, and which extends into the container holding the medication in solution. The rapid passage of the steam creates a vacuum in the tube, allowing the medication to be drawn up and expelled from the nozzle in a fine mist mixed with steam. Safety features include a valve to reduce excessive pressure, and an automatic cut-off of current when the water in the container has been completely utilized.

The combined steam-generator and aerosolizer has the following advantages²⁹: It is sturdy, compact and convenient for home, office or hospital use. It is inexpensive to operate. The technic is so simple that self administration is readily learned by the patient. One can aerosolize larger quantities with this than with the oxygen nebulizer method. Mixed aerosols are readily produced. It is practically fool-proof because of its safety features—there are no fire hazards as with the oxygen method.

The aerosol produced by this device may be administered by simple inhalation (as with the old-fashioned steam kettle), by confining the patient to

* Made by the Kaz Mfg. Co., 540 12th Ave., New York City.

a small chamber into which the aerosol is blown; by confining the aerosol in a tent covering the patient; and by confining the aerosol in a box from which the patient inhales (figure 2). Detailed descriptions of these methods, and the blood levels of penicillin obtained with each have been reported elsewhere.¹⁶ Suffice it to say that excellent therapeutic levels of penicillin—five

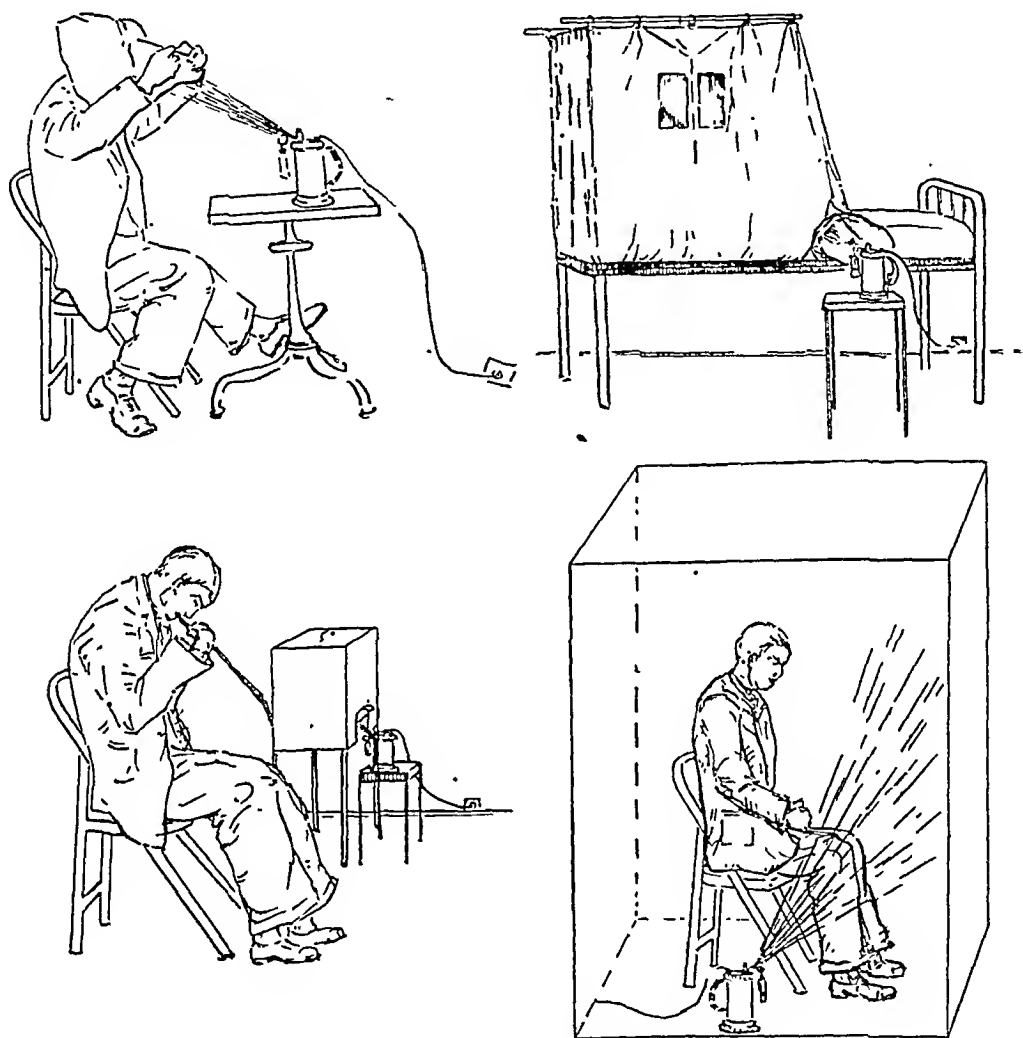


FIG. 2. Methods of inhalation of aerosols.

to six hours in duration—have been obtained using penicillin in propylene glycol, and the tent or breathing box for the purpose of confining the aerosol (table 1).

CLINICAL USES OF MEDICATED AEROSOLS

As indicated before, aerosol therapy for the treatment of respiratory diseases has assumed increasing importance in recent years. The first impetus was given by Graeser and Rowe, who introduced their nebulizer and a stronger epinephrin solution (1-100) for the treatment of asthma by inhala-

tion.³ Progress was furthered by the introduction of the continuous inhalation method, treating asthma with aerosols of epinephrin, vaponephrin, and neosynephrin.⁴ Subsequently, Stacey,⁵ and Applebaum⁶ utilized the identical procedure for the introduction of sulfonamides into the lung for the treatment of such respiratory infections as bronchitis, bronchiectasis and lung abscess, as well as asthma complicated by infection. A "smoke" of sulfa-thiazole in microcrystalline form was used by Chapple and his associates, experimentally and therapeutically in the treatment of respiratory infection.³⁰

With the advent of promin and its possible therapeutic value in the treatment of tuberculosis of the lung, Edlin and his associates attempted, without

TABLE I
Penicillin Blood Levels Obtained by Different Methods of Inhalation of Aerosols of Aqueous and Propylene Glycol Solutions of Penicillin

Method of Inhalation	Penicillin Dosage (Units)	Type of Aerosol	Penicillin Blood Levels (Oxford Units) Time in Hours						
			$\frac{1}{2}$	1	2	3	4	5	6
Open	50,000	Aqueous	.4	0	0	0	0	0	0
	100,000	Aqueous	1.2	1.0	.6	0	0	0	0
Tent	50,000	Aqueous	0	0	0	0	0	0	0
	100,000	Aqueous	.6	0	0	0	0	0	0
	50,000	Propylene glycol	.25	.031	.031	.031	.031	0	0
	100,000	Propylene glycol	.5	.5	.062	.031	.031	.031	0
Breathing box	50,000	Propylene glycol	1.0	1.0	1.0	1.0	1.0	1.0	.5
	100,000	Propylene glycol	1.0	1.0	1.0	1.0	1.0	.5	.5
	0 Control	Propylene glycol	.5	.5	.5	.5	.25	.25	.25

success, to cure tuberculosis by inhalation of promin aerosol.³¹ Barach and his associates had previously shown that promin aerosol could prevent experimental tuberculosis in guinea pigs.³²

When the rôle of penicillin in combating infection was demonstrated, simultaneous experiments were started with this drug in England³³ and in this country. Bryson, Sansome and Laskin produced aerosols of penicillin,²⁸ and this was applied clinically by Barach and his associates, utilizing the oxygen-nebulizer method.⁷ By the addition of special devices, Barach has also been able to treat infection in the sinuses with penicillin aerosol.³⁴

Streptomycin has, in some instances, succeeded in aerosol form where penicillin had failed, in the treatment of bronchiectasis.⁸

The steam aerosolizer described above made possible experiments with medications not readily amenable to aerosolization by the oxygen-nebulizer method, for the amount that can be placed into the nebulizer is limited (2 to 3 c.c.).

With this apparatus Prigal, Morganbesser and McIntyre³⁵ have shown the feasibility of the employment of penicillin aerosol for *prophylactic pur-*

poses as well as for therapy in infections of the respiratory tract. The use of penicillin aerosol during the early (virus phase) of an acute upper respiratory infection inhibits the bacterial phase, and such complications as sinusitis, bronchitis, bronchiectasis, and infective asthma. Similarly, penicillin and other aerosols should be of value prophylactically in the case of patients with rheumatic fever, glomerular nephritis, and other disease entities aggravated or induced by respiratory infections.

RESULTS OF EXPERIMENTS WITH MEDICATED AEROSOLS PRODUCED BY A STEAM AEROSOLIZER

As was described elsewhere,^{20, 29} initial experiments to explore the possibilities of the steam aerosolizer revealed that solutions of sodium sulfadiazine, penicillin, propylene glycol, aminophyllin, and epinephrin could be readily aerosolized.

Following the inhalation of sodium sulfadiazine aerosol, there was evidence of rapid and prolonged absorption of this drug. High blood levels (5 to 12 mg. per cent) were obtained in four patients within 30 minutes of inhalation of 50 c.c. of a 5 per cent solution (2.5 gm.) by the open method, despite the fact that considerable amounts were lost by dissipation into the atmosphere, and by condensation on the patient's face. These therapeutic levels were maintained for four hours in one patient, and six hours in another.²⁹ The estimations of sulfadiazine were made by a micro method using finger tip blood. More accurate determinations, using venous blood, were made jointly with Lehr, and these disclosed considerably lower blood levels of sulfadiazine, reaching a maximum of 1 to 1.5 mg. per cent, and lasting six hours. On the basis of these prolonged blood levels, following an aerosol treatment lasting about 15 minutes, it can be postulated that there may be temporary storage of the aerosol somewhere in the lung. Similar findings with penicillin-propylene glycol aerosols led to the same conclusion.¹⁶ Identical observations and conclusions were made by Chapple and Lynch,^{30b} who employed a "smoke" of sulfathiazole micro crystals, and demonstrated sulfathiazole in the circulation for at least six hours after treatment.

In the studies with penicillin,¹⁶ aqueous aerosols were at first employed, and were inhaled directly by the open method. Rapid absorption was noted by the blood studies, but this was of short duration. Attempts were made, therefore, to confine the aerosol. The tent method and breathing box, previously described, were found very suitable for this purpose. When the aerosol of penicillin was stabilized by dissolving the drug in propylene glycol, and by the addition of glycerine (5 per cent), highly effective blood levels of penicillin of long duration were obtained. Indeed, these levels (utilizing the micro method of Fleming³⁶) went beyond expectation, and so the experiments were repeated by another technician, utilizing another method for penicillin assay employing venous blood (Randall's method).³⁷ Unusually high blood levels of "penicillin" were obtained again. Control studies in

three instances indicate the possibility that propylene glycol aerosol, when inhaled, imparts some bactericidal properties to the blood, which accounts for some of the findings.¹⁰ This phenomenon is being investigated further (table 1).

At the suggestion of an associate, Dr. Leopold Lazarowitz, experiments were initiated on the action of insulin in aerosol form, using rabbits as the experimental animals.¹⁰ These animals were treated by the open method, and by confinement in air-tight chambers, and were exposed to aqueous and propylene glycol aerosols of crystalline insulin, in doses ranging from 400 to 1000 units, with but little reduction in the blood sugar (figure 3). This

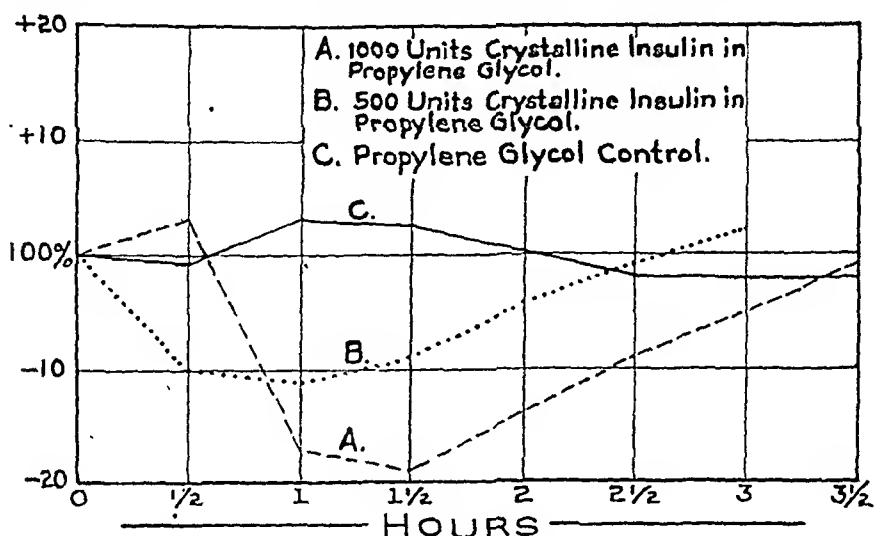


FIG. 3. The action of insulin aerosol on the blood sugar of rabbits.

reduction was never enough to convulse the animals, and occurred maximally in from one to one and one-half hours. Absorption was definitely delayed, as discussed earlier, due probably to the great molecular size of insulin. The possibility that the insulin was inactivated by the method of aerosolization was dispelled when the aerosol was condensed and, by injection of the condensate, convulsed the animal. The insulin aerosols were considered as being not practical for clinical application. The experiments with insulin were discontinued.

Our interest in asthma, and the possibility of aerosolizing large quantities of solutions rapidly with the steam aerosolizer, led to the investigation of aminophyllin in aerosol form in the treatment of this condition.³⁸ Forty adult patients were treated by this method, using (in most instances) one ampule containing 0.25 gm. of aminophyllin in 10 c.c. of water for a single treatment. Of these, 32 (80 per cent) responded favorably. Some of these patients were in status asthmaticus, and were unresponsive to epinephrin. In five instances there was a response to aerosol therapy after aminophyllin had failed by the intravenous route. This was remarkable since, by the use

of the open method, the patient actually inhaled only about 0.05 gm. of aminophyllin—a dose ordinarily considered ineffective by injection. The excellent results were probably due to the fact that the aminophyllin was brought directly to the site of action. This factor also accounted for the rapidity of action, relief being obtained, in the majority of cases, in a matter of minutes. By means of vital capacity determinations of nine patients before and after treatment, improvement was noted, ranging from 7.4 per cent to 56.9 per cent. The average increase was 20.6 per cent.

Control studies were undertaken with steam, and nine patients inhaled the steam produced by the apparatus. In some instances, the vital capacity studies revealed improvement running as high as 11.1 per cent. Some, however, were definitely worse following steam inhalations. The average increase in vital capacity of these cases exposed to steam was 2.4 per cent.

Another experiment performed was designed to compare the relative efficiency of the inhalation method as compared with the intravenous administration of aminophyllin. Nine patients were treated with 5 c.c. of aminophyllin (0.125 gm.), half the usual dose, intravenously, and vital capacity observations were made before and after treatment. These showed improvement ranging from 6 per cent to 20 per cent. The average of 11.9 per cent was about half that obtained by the aerosol method.

To eliminate the possibility of psychogenic factors playing some rôle in these aerosol experiments, ammonium chloride (10 c.c. of a 5 per cent solution) was substituted for the aminophyllin, and this unexpectedly resulted in considerable increase in the vital capacity. This may be explained by the solvent action of this chemical on the tenacious sputum found in asthmatic patients. Ammonium chloride aerosol is now in use as an adjuvant to the aminophyllin therapy; a combined aerosol is frequently administered.

It is of interest to note that no untoward reactions to the inhalation of aminophyllin were observed, whereas one patient suffered a vasomotor collapse after administration of 4 c.c. of this drug intravenously.

In view of the frequent association of infection (sinusitis, bronchitis and bronchiectasis) with asthma, a number of patients were treated with penicillin aerosol as well as aminophyllin.³⁵ This was best done after aminophyllin, or aminophyllin and ammonium chloride combined had been inhaled. This increased the vital capacity and enhanced the patient's ability to inhale the penicillin aerosol. The tent and breathing box, confining the aerosol, were employed where penicillin was indicated because it gave better penicillin blood levels. These studies, as well as the prophylactic application of penicillin aerosol in infective asthma, are continuing.

SUMMARY AND CONCLUSION

Due to the anatomical structure of the lung, providing it with a very large surface for absorption, and because the lungs embryologically stem from the gastrointestinal tract, it was to be expected that highly effective

absorption of aerosols through this organ would take place. What was not anticipated was the observations indicating that there may be temporary storage of the aerosols somewhere in the lungs. This is the only way to account for the prolonged blood levels obtained with sulfadiazine and penicillin.

These observations have led to the conclusion that other medications in aerosol form may possibly be introduced through the lungs *for systemic purposes*. It may thus be possible to use the penicillin in aerosol form, not only to combat local bronchopulmonary infection, but for the treatment of bacteremias and for infections elsewhere in the body responsive to antibiotic therapy.

It is advantageous to introduce medications in aerosol form via the lung, since one obviates, as in the case of penicillin, possible destructive action by the gastric juices. There are limitations, however. Aerosols of substances of high molecular structure, such as insulin, do not readily pass the lung barrier as compared with the simpler compounds of sulfonamides or penicillin. Extreme care must also be used in selecting material for aerosolization, because of possible injury to the lung as in the case of strong acids or other noxious agents. The possibility of sensitivity to a specific aerosol, and the induction of asthma or other types of allergy, must also be borne in mind. It is noteworthy, however, that there have been very few allergic reactions to penicillin aerosol in the treatment of over 200 patients.

For effective therapy, it is necessary to form a stable aerosol of small particles— $2\ \mu$ or less. The apparatus producing the aerosol should be easy to handle, fool-proof, available for home use, inexpensive and capable of aerosolizing large quantities of solution when necessary. These requirements are satisfied by the combined steam-generator and aerosolizer used in these studies. With this apparatus very high blood levels of penicillin of long duration have been obtained. The penicillin was dissolved in propylene glycol to produce a more stable aerosol. Possibly, the glycol exerts some penicillin-like action. Patients treated with penicillin-propylene glycol aerosol receive maximum effect, according to blood studies, by using a tent over the patient, thus confining the patient in an atmosphere of penicillin, or by confining the aerosol in a box from which the patient may breathe the aerosol.

The aerosol method, according to these observations, may replace therapy by injection when using penicillin. This should be of particular advantage in the treatment of infants and children, or where prolonged treatment is indicated as in subacute bacterial endocarditis. Here, repeated painful injections, or continuous intravenous drips with all their objectionable features, may be obviated.

The studies on patients with asthma have disclosed that the aerosol method of administering aminophyllin may, at times, succeed even after failure of aminophyllin given intravenously. This is striking, since it has been estimated that about 0.05 gm. of aminophyllin is introduced by the open

inhalation method—a dose which is ordinarily considered ineffective intravenously.

As a by-product of these studies, it has been observed that ammonium chloride by inhalation (10 c.c. of 5 per cent solution) has also been of help in treating asthma, perhaps because of its solvent action on the thick tenacious mucous plugs characteristically found in this condition. Where an associated bronchiectasis or bronchitis exists along with asthma, preliminary treatment with a mixed aerosol of aminophyllin and ammonium chloride is followed by treatment with aerosol of penicillin.

This review of what was previously reported in studies of absorption through the lungs, as well as the presentation of recent studies with aerosol therapy, serves to call attention to the possible use of this organ as a means of introduction of medication, not only for the treatment of local bronchopulmonary diseases, but for systemic action as well.

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THE RÔLE OF PREVENTIVE MEDICINE IN CLINICAL PRACTICE *

By WILSON G. SMILLIE, M.D., *New York, N. Y.*

THE text of this discussion—perhaps theorem is a better word—is that the internist of the next generation must concern himself primarily with the field of preventive medicine. This statement carries no implication that all physicians will soon be employed on Federal salary, or will be busy in the intricacies of public health administration.

Let us make a clear distinction between public health and preventive medicine. *Public health* is the obligation of the community to protect its members against the hazards of communal living, and to promote community-wide health. Thus public health is not a function of the internist, nor his direct responsibility. *Preventive medicine* is the obligation of the individual to protect and promote the health of himself and his family. But each individual needs expert guidance in these matters. It is a function of the physician to provide the advice and to give each individual suitable protection.

It may be emphasized at the outset that this discussion is not concerned with the physician who has had a long and successful career in internal medicine. His work is nearly done. His methods cannot be modified. But we are concerned with the young internist who is just beginning his life's work.

In addition, these remarks are addressed to the teacher—to those who train the potential internists of the next generation. Often the teacher makes the serious mistake of training his students for the type of service that he, himself, has given in the past. Obviously this mistake must not be made. The young internist must be prepared not for the type of medical practice of the past generation, nor in fact the practice of medicine of the present time. One must attempt to forecast the future, and then try to train the young medical man to meet and to solve the problems that he will encounter in the next generation. Therefore each medical teacher must first ask himself: "What will be the nature of medical practice during the next 30 to 50 years?"

The forecasting of the future of medicine is not as difficult as it may seem at first glance. One cannot draw in all the fine details, but the broad outlines of the picture are quite clear. We may follow the technic of the historian, the economist, the geneticist, and the ecologist, and by extension of well-defined trend lines, we can map out the future with a fair degree of accuracy.

The first important trend will be a continuation of our change from an agricultural and pastoral people to a highly industrialized economy, with all

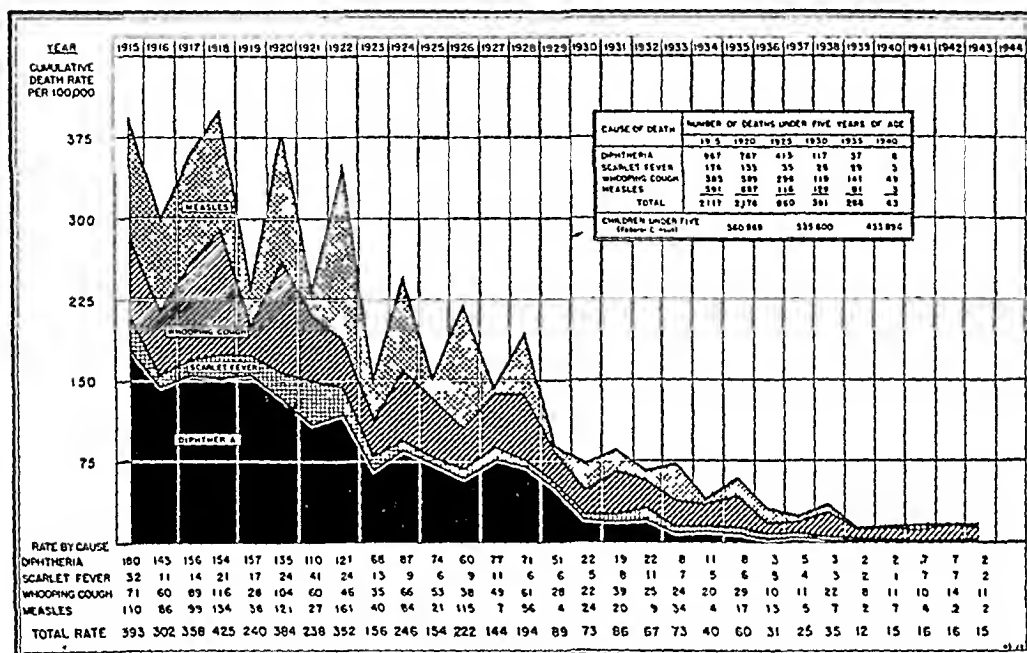
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From the Department of Public Health and Preventive Medicine, Cornell University Medical College, 1300 York Avenue, New York City.

the changes in our social structure and family life that these economic changes entail.

Diseases due to the hazards of the industrial processes, and to the great complexities of industrial life, will increase in prevalence and importance.

There will continue to be a marked diminution in illness and death that is produced by infectious processes (figure 1). This will include the infectious diseases of childhood, respiratory infections, all the pneumonias, as well as pulmonary tuberculosis, and perhaps syphilis.



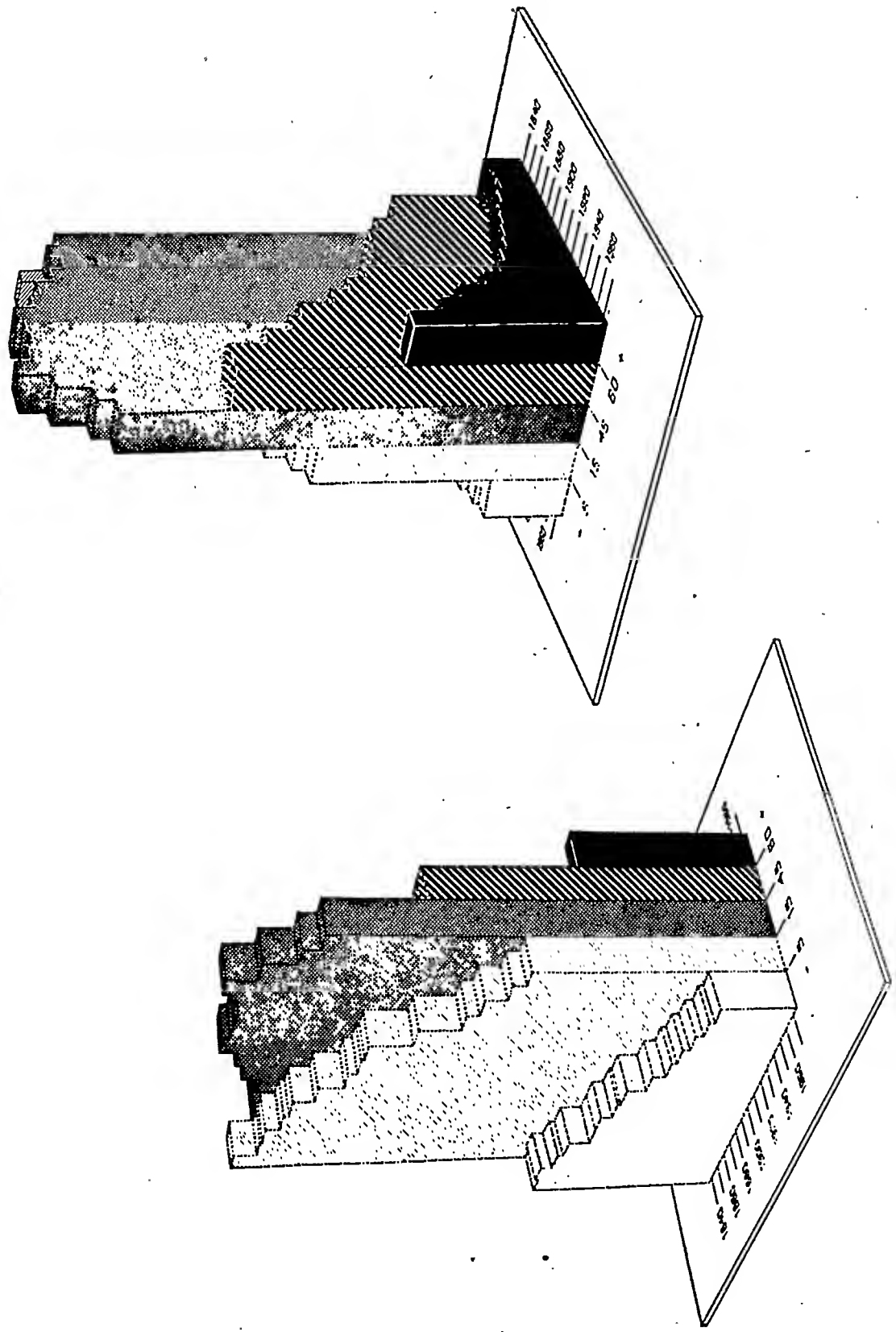
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FIG. 1. Decline in infectious disease mortality, New York: 1915 to 1944.

Mental disease will increase. Furthermore, it will occur predominantly in the older age groups. There will be much greater demand for facilities for institutional care of mental illness.

The most important trend is that of an aging population (figure 2). By the year 1980, the composition of the American population will be markedly changed. There will be a strong shift from the younger to the older age groups. We shall have fewer infants and children, and a much larger number of people in the older age groups.

These changes in population will result in a marked increase in the degenerative diseases, particularly in diseases of the heart and the circulation. Cancer will increase, as will diabetes and arteriosclerosis. This increase will be due, in great part, to the changes in the composition of our population, and to a lesser degree, to changes in the national economy and the social struc-



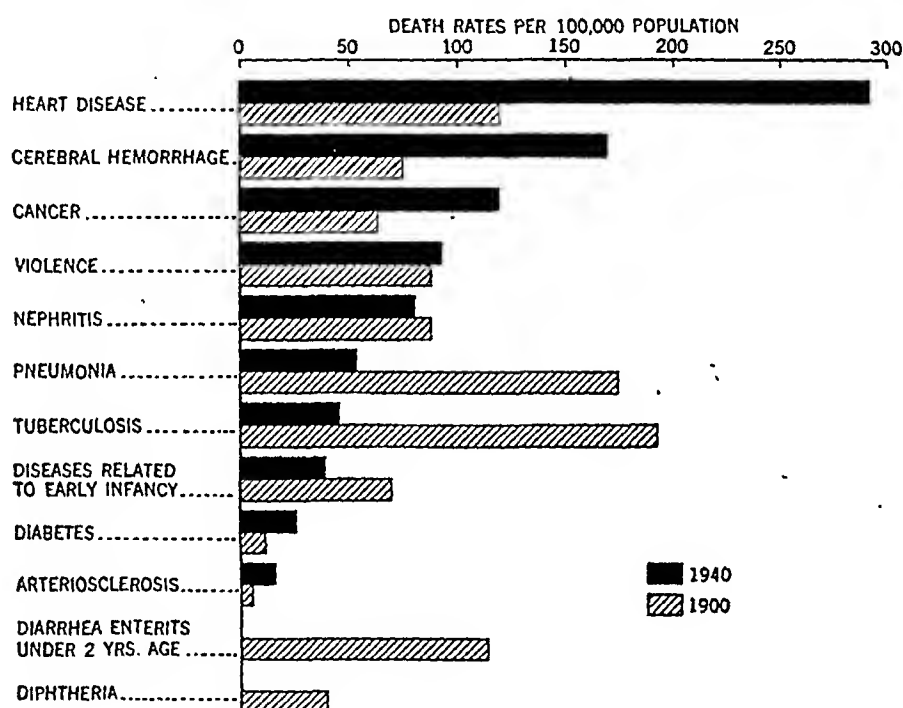
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FIG. 2. Our aging population: 1840 to 1980.

ture. In all tabulations of vital statistics, the degenerative conditions will be overwhelmingly important as causes of illness and death (figures 3 and 4).

If our foresight is accurate, then major emphasis in internal medicine during the next 30 to 50 years must be placed on methods that shall be employed in the prevention of the ravages of chronic debilitating disease. The following methods may be employed:

1. Active research, with a development of better understanding of the *primary causes* of degenerative diseases. This must include mental disease.
2. Development of suitable methods for early detection of the degenerative diseases.



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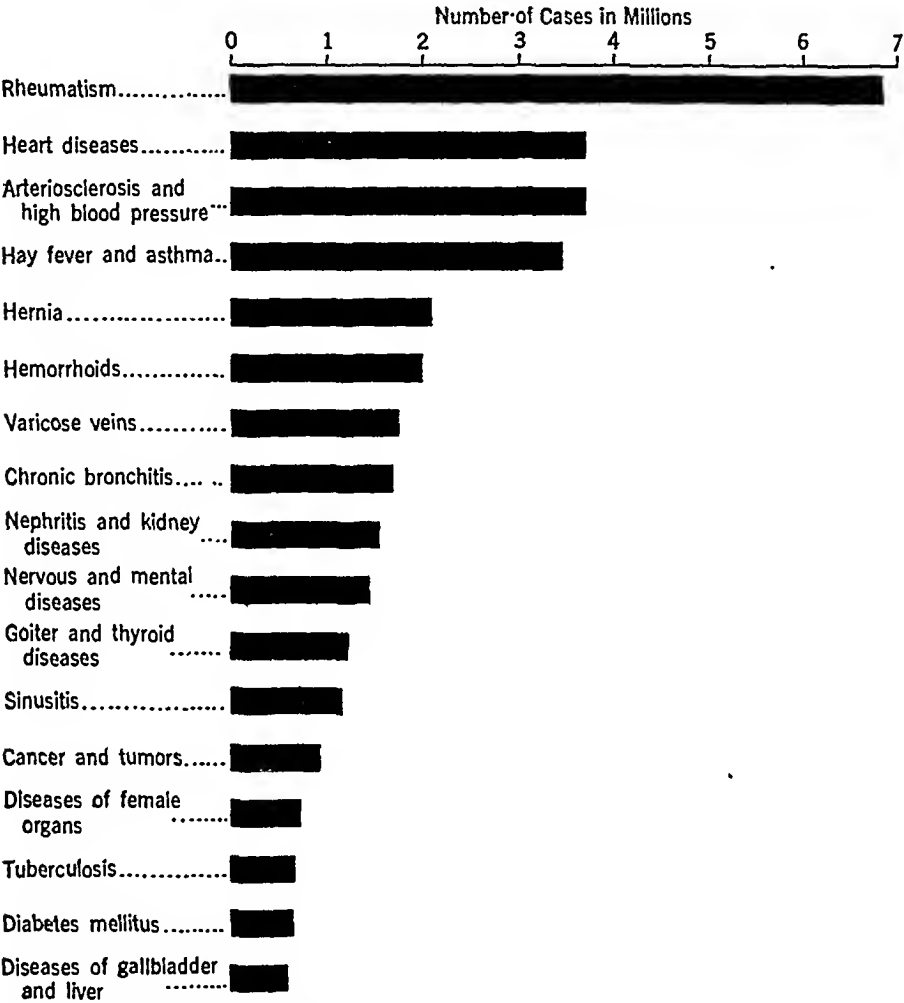
FIG. 3. Death rate from 10 leading causes of death in the United States: 1900 compared with 1940.

3. Rehabilitation, i.e. formulation of programs that will promote suitable life adjustment for those in whom degenerative disease has become manifest.

It is quite clear that all these activities lie within the realm of preventive medicine, for curative medicine will be of little avail. The degenerative diseases, as manifested in individuals past middle life, are, for the most part, not curable. The damage has been done to the tissues and is not repairable. The course of the disease is not reversible; function is permanently impaired, and structure is destroyed. Often these patients do not respond favorably even to palliative therapeutic measures.

It must be remembered that degenerative diseases have their inception early in life. Therefore, if our predictions are correct thus far, it becomes

obvious that the primary functions and major activities of the internist of the coming generation will be in the field of preventive medicine, and will be most effective for individuals of the third and fourth decades of life (figure 5). Primary causes of degenerative diseases must be determined, and very early detection must be sought as the major goal.



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FIG. 4. Estimated prevalence of specified chronic diseases in the United States (1937).

It is quite clear also that the preventive measures in degenerative diseases must be applied by the *individual practitioner* of medicine, and not by traditional public health procedures.

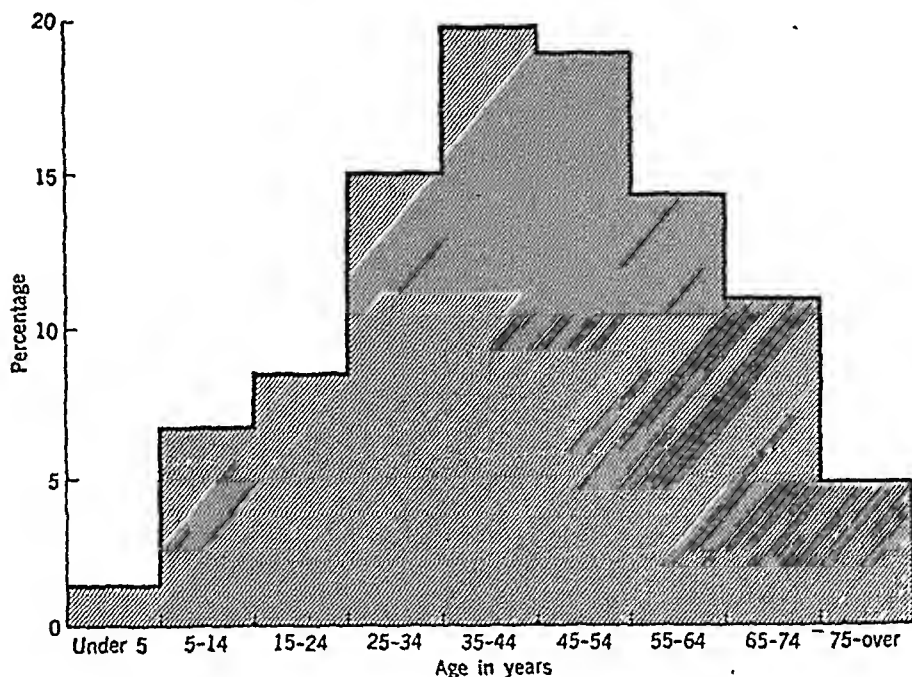
Most of the gains that have been secured in the lowered death rate have been due to improvement in infant mortality, and to a reduction in communicable disease. These benefits have been secured by the mass method of attack. It has seemed logical therefore to attempt to apply the same principle of the mass method of attack in the control of degenerative diseases.

For the most part, one may predict that these technics will not be success-

ful in a reduction of the general death rate, nor in the prevention of illness that is due to degenerative diseases.

It is probable that certain well-tried and proved public health measures may be utilized effectively in the control of degenerative diseases. The following examples may be cited:

(a) Methods of popular education may be employed, by means of which the great mass of the people can be kept informed concerning advances that are made, by science, in early diagnosis, and also concerning new procedures for control of disease. These public health education technics require a



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FIG. 5. Percentage distribution of persons in the U. S. with chronic disease or permanent impairment, according to age groups, estimated in 1937, showing the high prevalence of invalidism in the fourth decade.

greater degree of skill and more control than has been exercised in the past. They are very useful measures if employed intelligently, but may do more harm than good.

(b) Organization, under community auspices, of special facilities for the medical care of the poor. By this means the community makes available to all, adequate facilities for prevention and amelioration of degenerative disease.

(c) The development, by accepted public health methods, of adequate community-wide facilities for comprehensive medical care of all the people.

These and other technics may be applied by the community on an organized "public health" basis, in an effort to aid in the control of degenerative diseases. It is obvious, however, that these procedures are, at best, quite

incomplete and faulty, and that the mass method of attack upon the degenerative diseases will not be very effective.

The prevention of the degenerative diseases will be secured by attrition, rather than by concerted mass action. Each person is an individual problem, requiring a complete personal understanding, and a confidence between physician and patient. Thus prevention of the degenerative diseases becomes a private rather than a public matter. It requires an individual exchange of ideas, plans, and confidences. This necessitates a continuity of care, over a long period of time, and with a knowledge of all the factors that impinge upon the patient's life: his occupation, his home life, his recreations, his previous illnesses, his attitudes toward life, and his reactions to adversity. This type of medical care requires a continuous individual and very personal medical record which is kept through many years. It also requires a continuous personalized medical service.

If our thesis is correct, then the internist of the future, if he is to be effective and successful in his chosen life work, must have been trained to observe, and to think in terms of the preventive aspects of disease. He must place as much emphasis upon prevention, in the care of his patients, as he now does upon diagnosis and therapy. He must be interested, not only in those who are sick, but in those who are well. His primary interest must be in the young, normal, presumably healthy man, during the formative periods of life, for here his efforts can be most fruitful. Here lie the opportunities for the future of medical practice. This point of view is in great contrast to the present practice, in which the internist devotes most of his time to the infirmities of the aged, to the irreparably damaged individual whose life history has been written, and whose book of life has, for all practical purposes, been closed.

The young internist must also be thoroughly aware of the changing social concepts that are influencing the social and economic future of the nation. He should, I believe, receive formal training in this field. He must be as well aware of the social structure of the family, and of the community, as he is now familiar with the physical structure of the human body. For the internist of the next generation will deal primarily with *people*, and not primarily with *disease*. Thus a sound knowledge of economics and of sociology is as important a premedical course as is required work in chemistry, physics and physiology.

Thus we end our brief presentation as it began, with a reiteration of our prophecy: The internist of the future must become a practitioner of preventive medicine, working primarily with people who are not ill. If this theorem is correct, then the young internist who is just beginning his life work, should prepare himself to meet this responsibility.

BRUCELLA ANTIBODIES FOLLOWING CHOLERA VACCINATION *

By C. WESLEY EISELE, M.D., F.A.C.P., NORMAN B. McCULLOUGH, Ph.D.,
M.D., and GRACE A. BEAL, *Chicago, Illinois*

BRUCELLA agglutinins appearing after vaccination against cholera have been reported to occur in six of seven individuals.¹ We have suggested that this phenomenon may be a source of confusion in the diagnosis of brucellosis inasmuch as the agglutination test is widely used for this purpose and several million veterans received cholera vaccine during their military service. The present studies were undertaken to determine further the effects of cholera vaccination on brucella agglutinin production and to observe the effects on the opsonocytophagic test and on the brucellergen skin test.

METHODS AND MATERIAL

Twenty volunteers were selected who with one exception had negative agglutination tests, opsonocytophagic tests, and brucellergen skin tests. The volunteers were all young adults and were drawn largely from medical students and laboratory technicians. Following preliminary testing, they were given the standard two-dose cholera vaccination (0.5 c.c. and 1.0 c.c. doses one week apart) using a commercial vaccine each c.c. of which contained 8 billion killed *Vibrio comma*. Agglutination tests, opsonocytophagic tests, and intradermal brucellergen skin tests were made at intervals after the vaccination. With minor exceptions, the tests were made at approximately two or three weeks, eight weeks, 18 weeks and at one year. The agglutination tests were performed by the standard test tube method as well as by the rapid slide method.² The opsonocytophagic tests and the brucellergen skin tests were performed by the methods of Huddleson.²

RESULTS

The results of the three tests before and at intervals after cholera vaccination are presented in table 1.

Before cholera vaccination, 19 of the 20 subjects were entirely negative to all three tests. In one subject the brucellergen skin test was moderately positive, but the agglutination and opsonocytophagic tests were negative.

The agglutination tests became positive after cholera vaccination in all 20 of the individuals. Sixteen or 80 per cent were positive in titers of 1/40 or higher; 12 or 60 per cent were positive in titers of 1/160 or higher; and 9 or 45 per cent were positive in titers of 1/320 or higher. One individual de-

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From the Department of Medicine, School of Medicine, University of Chicago.
Aided in part by a grant from Swift and Company.

TABLE I
Brucella Antibody Response Following Cholera Vaccination

Sub- ject No.	Before Cholera Vaccine				After Cholera Vaccine											
					2 or 3 Weeks				8 Weeks				18 Weeks			
	Aggl. Test	Opsonic Test	Skin Test		Aggl. Test	Opsonic Test	Skin Test		Aggl. Test	Opsonic Test	Skin Test		Aggl. Test	Opsonic Test	Skin Test	
1	neg.	0-0-0-25	neg.		1/160	21-4-0-0	neg.		1/160	19-3-3-0	neg.		1/80	25-0-0-0		
2	neg.	0-0-0-25	neg.		*1/160	20-5-0-0	neg.		1/320	20-2-3-0	neg.		1/40	0-0-6-19		
3	neg.	0-0-0-25	$\frac{1}{4} \times 1$		*1/320	22-2-1-0	1×1		1/160	25-0-0-0	1×1		1/40P	11-14-1-0		
4	neg.	0-0-0-25	neg.		1/80	23-2-0-0	neg.		1/80	25-0-0-0	neg.		1/160	20-5-0-0		
5	neg.	0-0-0-25	neg.		*1/320	23-2-0-0	neg.		1/320	19-4-2-0	neg.		1/80	25-0-0-0		
6	neg.	0-0-0-25	neg.		*1/320	12-9-4-0	neg.									
7	neg.	0-0-0-25	neg.		*1/320	22-2-1-0	neg.		1/320	17-5-2-1	neg.		1/80	1-5-10-9		
8	neg.	0-0-0-25	neg.		1/20	0-0-0-25	neg.		1/20	1-1-14-9	neg.					
9	neg.	0-0-0-25	neg.		*1/20	0-1-17-7	neg.		1/20	0-0-8-17	neg.		1/20	2-4-7-12		
10	neg.	0-0-0-25	neg.		*1/160	6-10-9-0	neg.		1/160P	23-1-1-0	neg.		1/40	17-6-2-0		
11	neg.	0-0-0-25	neg.		*1/40	0-0-4-21	neg.		neg.	0-0-0-25	neg.					
12	neg.	0-0-0-25	neg.		neg.	0-0-0-25	neg.		1/20	0-0-1-24	neg.		neg.	0-0-0-25		
13	neg.	0-0-0-25	neg.		1/2560P	23-2-0-0	neg.		1/1280	25-0-0-0	neg.		1/640	22-1-2-0		
14	neg.	0-0-0-25	neg.		1/40	25-0-0-0	neg.		1/40	0-0-2-23	neg.		neg.	0-0-0-25		
15	neg.	0-0-0-25	neg.		1/20	8-5-9-3	neg.		1/20	1-4-17-3	neg.		neg.	0-0-0-25		
16	neg.	0-0-0-25	neg.		*1/80	22-3-0-0	neg.		1/40	0-2-7-16	neg.		neg.	0-0-0-25		
17	neg.	0-0-0-25	neg.		*1/320	21-3-1-0	neg.		1/160	25-0-0-0	neg.		1/80	16-2-3-4		
18	neg.	0-0-0-25	neg.		1/320P	21-2-1-1	neg.		1/160	6-12-6-1	neg.		1/320	15-10-0-0		
19	neg.	0-0-0-25	neg.		1/40	18-4-2-1	neg.									
20	neg.	0-0-0-25	neg.		*1/320	22-1-2-0	neg.									

* Tests done 2 weeks after vaccination.

P = partial agglutination.

Skin tests recorded as size of induration in inches at 48 hrs.

veloped a persistently high titer which reached 1/2560 partial and 1/1280 complete. The titers were maximal either at the two or three week test or at the eight week test, and thereafter declined. At the one-year post-immunization tests, six of the 14 subjects examined still had positive tests in dilutions ranging up to 1/160. Generally speaking, those with the highest peak titers tended to show greater persistence of antibodies.

The opsonocytophagic test became positive after cholera vaccination in 16 or 80 per cent of the subjects, and in most instances the degree of positivity tended to parallel the agglutinin titer. The tests of 13 or 65 per cent of the subjects showed marked phagocytosis by 80 to 100 per cent of the cells, a response usually considered as indicating good resistance to the infection. Some opsonic activity persisted for one year in most of those individuals in whom the agglutination test also remained positive.

The brucellergen skin test continued to be negative after cholera vaccination in the 19 individuals who had negative pre-immunization tests. In the one subject whose skin test was positive before receiving cholera vaccine, the test retained the same degree of positivity at two weeks and at eight weeks after vaccination.

DISCUSSION

It has been demonstrated that brucella agglutinins may be engendered in high titers by cholera vaccination in a majority of individuals so treated. In some, significant titers persist for a year or more. In a survey of 100 individuals who had been vaccinated against cholera while in military service,³ 56 per cent had positive brucella agglutination tests in titers of 1/20 or higher; 41 per cent were positive in titers of 1/40 or higher; and 20 per cent were positive in dilutions of 1/80 or 1/160. In the group who were tested 18 to 28 months after vaccination, 27 per cent still had titers of 1/40 or 1/80.

Although it has not been demonstrated, one may reasonably expect that many months after the original brucella agglutinins have disappeared from the circulation, significant titers may recur as an anamnestic response to the stimulus of a non-specific febrile illness.

Some three million veterans who were vaccinated against cholera while in military service have returned to civilian life. Unless the fact becomes widely recognized that brucella antibodies may be engendered by cholera vaccination, that they may persist for many months and perhaps may recur after a lapse of years, further confusion is likely to be added to the often perplexing problem of the diagnosis of brucellosis.

The diagnosis of chronic brucellosis frequently is a difficult task which may tax the ability of the best of physicians. There are no pathognomonic symptoms, few physical signs, and except for the recovery of the causative organism which usually is difficult during the chronic stage, there are no completely reliable laboratory tests.

The agglutination test is the most widely used procedure for the diagnosis of brucellosis. We previously discussed sources of difficulty which may arise

in the performance and interpretation of this test.^{4, 5} The present data suggest a further limitation on its application. An agglutinin titer of 1/80 or 1/160 is commonly, although deplorably, accepted as confirmation of a diagnosis of brucellosis in the presence of a great variety of symptoms. In the recently enacted occupational disease legislation in Iowa,⁶ brucellosis has been made a compensable disease in certain occupations. The law provides that agglutination titers of 1/160 on two successive tests may be considered as verifying a clinical diagnosis of brucellosis. The symptoms of the chronic disease are notoriously vague and diffuse. One author⁷ has listed 150 symptoms and manifestations which have been observed during the course of chronic brucellosis, and it is common knowledge that close similarity exists between the symptoms of this disease and those of the psychoneuroses. The pitfalls of such legal definitions of diagnostic criteria become obvious in the light of the vagaries of the disease and recognized uncertainties of the agglutination test.^{4, 5} As an example, most of the subjects of the present investigation would meet the immunological requirements of this legal definition.

The opsonocytophagic test is not as widely used as the agglutination test. Nevertheless, the production of brucella opsonins by cholera vaccination may in some instances be misleading to the physician.

In studies on the antigenic interrelationship of *Vibrio comma* and brucella, we have shown that this cross-antibody response is due to an H antigen of *Vibrio comma*.^{1, 8}

The fact that cholera vaccine does not cause a positive brucellergen skin test may be of aid in differentiating the source of brucella antibodies in doubtful cases. Further aid may be obtained by absorption tests with cultures of *Vibrio comma* and of brucella.

Consideration is being given to the possibility that cholera vaccine may be useful in immunologic procedures of value in brucellosis—a protective vaccine for those occupationally exposed as well as a vaccine for the treatment of the chronic disease. The brucella antibody response as far as agglutinins and opsonins are concerned is at least as good as one would expect from any brucella vaccine or product. If the development of these antibodies can be shown to be correlated with resistance to infection with brucella, the use of cholera vaccine for prophylaxis and for therapy would be reasonable. Most workers agree that agglutinins do not measure resistance in brucellosis. Opsonins probably do in some degree measure specific resistance. Other antibodies, such as bactericidins may be important. The rôle of allergy is unknown but possibly considerable. If cholera vaccine afforded an effective protection against brucellosis, there would be obvious advantages over brucella vaccines in that subsequently one would be able to in part differentiate between antibodies produced by the vaccine and those produced by a suspected brucellosis. This could be accomplished by the brucellergen skin test or by resort to absorption tests.

SUMMARY

1. Twenty individuals with previously negative tests were given the standard immunization against cholera. The brucella agglutination test became positive in all of these individuals; in 80 per cent the titer rose to 1/40 or higher; in 60 per cent to 1/160 or higher; and in 45 per cent to 1/320 or higher.

2. The brucella opsonocytophagic test became positive in 80 per cent of the subjects. In 65 per cent the test showed marked phagocytosis by 80 to 100 per cent of the cells.

3. The brucellergen skin test remained negative.

4. Brucella agglutinins and opsonins were demonstrable in significant titer in a number of these individuals after the lapse of one year.

5. Unless it becomes widely recognized that brucella antibodies arise after cholera vaccination, further confusion may occur in the diagnosis of chronic brucellosis.

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CASE REPORTS

ADRENAL MEDULLARY TUMOR (PHEOCHROMOCYTOMA); CASE REPORT WITH SUCCESSFUL OPERATION *

By WILLIAM C. BURRAGE, Captain, M.C. (AUS). *Portland, Maine*, and
JAMES A. HALSTED, Major, M.C. (AUS), F.A.C.P.,
Boston, Massachusetts

THE clinical picture associated with functioning tumors of the adrenal medulla has been well described,^{1, 2, 3} leading to an increasing accuracy in diagnosis. Operative intervention is usually successful in correcting the leading physiological abnormality of paroxysmal hypertension.

In 1941 Biskind, Meyer, and Beadner⁴ reviewed the literature, analyzing a total of 29 cases which had come to operation. Since that time 22 additional cases have been reported⁵⁻¹⁹ (table 1). Of these 51 cases 11 died postopera-

TABLE I

	Cases	Living	Dead
Brunschwig and Humphreys, 1940 ⁵	1	1	
Hamilton, 1940 ⁶	1	1	
Biskind, Meyer, and Beadner, 1941 ⁴	29	23	6
Heath, Cahill, and Atchley, 1941 ¹⁰	1	1	
Engel, Mencher, and Engel, 1942 ¹¹	1	1	
Hyman and Mencher, 1943 ⁷	2	2	
Tennenbaum, 1943 ⁸	1	1	
Kenyon, 1943 ⁹	1	1	
Thorne, Hindle, and Sandmeyer, 1944 ¹²	1		1
Kvale, Roth, Claggett, and Dockerty, 1944 ¹³	1	1	
Duncan, Semans, and Howard, 1944 ¹⁴	1	1	
MacKeith, 1944 ¹⁵			
Keyser and Walters, 1924	1		1
Volhard, F., 1931	1		1
Oby and Protrowsky, 1933	1	1	
Bell and Powell, 1934	1		1
Hatieganu et al., 1939	1		1
Volhard, 1944 ¹⁶	1	1	
Mortell and White, 1945 ¹⁷	1		1
Roth and Kvale, 1945 ¹⁸	2	2	
DeVries, Mandl, Rachmilevitz, and Ungar, 1946 ¹⁹	1	1	
Authors' case, 1946	1	1	
Total:	52	40	12

tively, and one died of metastases two years after operation. Most of the remaining 39 patients were relieved of both signs and symptoms resulting from the functioning of these tumors. In three cases the tumors were malignant,^{9, 12, 15} the remainder being benign.

We have observed a patient with a pheochromocytoma of the left adrenal gland which was successfully removed, and in which the diagnosis was first sug-

* Received for publication January 3, 1947.

From the Medical Service, Sixth (U. S.) General Hospital.

gested by the patient's abnormal response to histamine phosphate. This case is reported because of the rarity of the tumor and because of certain data obtained regarding response to histamine.

CASE REPORT *

A 32 year old single paratrooper entered the Sixth General Hospital at Casablanca, French Morocco, on June 9, 1943, with the chief complaint of postprandial epigastric pain of nine months' duration. He had enjoyed normal health during his civilian life when he was employed as a salesman prior to his induction into the U. S. Army on June 9, 1942.

In September 1942 he began to suffer from dull gnawing mid-epigastric pain, which occurred approximately two hours after eating, and which was relieved by the intake of food or soda. His symptoms had not incapacitated him, and although he had attended sick call, he had not been hospitalized for this complaint until his present admission.

Since October 1942 he had noted temporary but mild pulsating post-occipital headaches which lasted 10 to 15 minutes, and were associated with slight palpitation, dyspnea, sweating and nervousness. These attacks occurred about once a month, but failed to show any apparent relationship to exercise, emotion, position, or the functioning of any other of his bodily systems. In fact, he had never noted any unusual symptoms even after several parachute jumps. He had never consulted a medical officer for these symptoms. In February 1943 at Fort Benning, Georgia, he developed the "grippe" during which he suffered a more severe headache than on any previous occasion. This had caused him to "shake all over" and he "could hardly breathe."

In May 1943 he developed an upper respiratory infection during which he suffered a similar severe headache. At sick call the following day a fever of 102° was found, and he was admitted to a nearby evacuation hospital. During this admission the presence of a duodenal ulcer was considered and was confirmed by a roentgen-ray examination. A gastric analysis was reported as showing no free hydrochloric acid. The patient recalled that, although the administration of 0.5 mg. of histamine phosphate subcutaneously was followed by a very severe pulsating headache, he had failed to report it. He was placed on an ulcer regime which improved his gastric symptoms and he was transferred to the Sixth General Hospital for disposition proceedings.

On admission the physical examination revealed a well nourished male of wiry build. Examination of the head, eyes, throat, and neck was normal. The heart showed no evidence of enlargement, murmurs, nor abnormal rhythm. The blood pressure was 120 mm. of mercury systolic, and 82 mm. diastolic. The pulse rate was 72 per minute and the rhythm was regular. Abdominal examination was not remarkable except for moderate tenderness in the epigastrium. No organs or masses were palpable. The remainder of the examination was negative. Roentgen-ray examination of the chest showed the heart to be of normal size and configuration. The duodenal cap showed a constant deformity, but no active ulcer crater could be demonstrated. The laboratory examinations of the blood, urine, and stool were within normal limits.

On June 11, 1943, a gastric analysis was performed because achlorhydria had been reported at the previous hospital. At 10:00 a.m. 1 c.c. of histamine phosphate

* We are greatly indebted to Col. John T. King, M.C. (AUS), of the Medical Service of Walter Reed General Hospital, and to Col. Lloyd G. Lewis, M.C. (AUS), of the Urological Service, for permitting us to report the observations made at that hospital, and for sending us complete notes of the patient's hospital admission, as well as sections and photographs of the tumor.

(0.5 mg.) was administered subcutaneously in the usual fashion. Five minutes later the patient developed marked flushing of the face and trunk with severe cramps in the upper abdomen, and complained of shortness of breath and a very severe headache. One of us (J. A. H.) saw the patient immediately thereafter, finding him to be pale, dyspneic, sweating profusely and complaining bitterly of a severe headache. At this time the blood pressure was 260 mm. systolic and 160 mm. diastolic. The pulse was regular, small, with a rate of 140 beats per minute. The above symptoms were followed by nausea and vomiting, but subsided in about 10 minutes. He then felt exhausted and weak. The following blood pressure and pulse observations were made:

Time	Blood Pressure	Pulse Rate
10:10 a.m.	260/160	140 regular
10:20 a.m.	220/130	120 regular
10:28 a.m.	180/100	96 (frequent extrasystoles)
11:00 a.m.	160/100	68 (occasional extrasystoles)
1:00 p.m.	95/60	74 regular

Because of this unexpected response, continued blood pressure observations were made which showed striking variations from a basal level of 100 to 120 mm. systolic and 60 to 80 mm. diastolic to sudden rises as high as 280 mm. systolic and 150 mm. diastolic. These lasted for periods of five to 10 minutes (figure 1). Once the presence of paroxysmal hypertension had been established, a search for a functioning adrenal medullary tumor (pheochromocytoma) was undertaken.

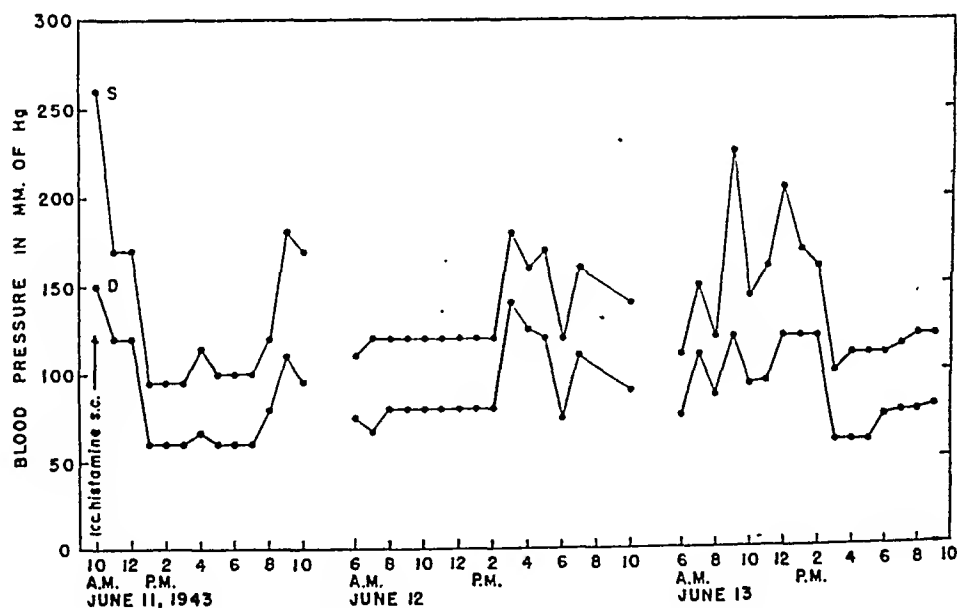


FIG. 1. Paroxysmal hypertension, Case K. G. Pheochromocytoma, left adrenal gland.

An electrocardiogram taken two days after this reaction showed evidence indicative of a coronary disturbance manifested by an abnormal T_1 with slight late inversion. On the third day late inversion of T_1 , T_2 , and T_4 and an elevated S-T interval in Lead IV were found. On the eleventh day after the reaction the electrocardiogram had returned to normal limits (figure 2).

An insulin tolerance test was performed which produced a profound hypoglycemic reaction with an associated hypertensive crisis as shown in the accompanying chart (figure 3). A cold pressor test was not remarkable and failed to produce an abnormal blood pressure response.

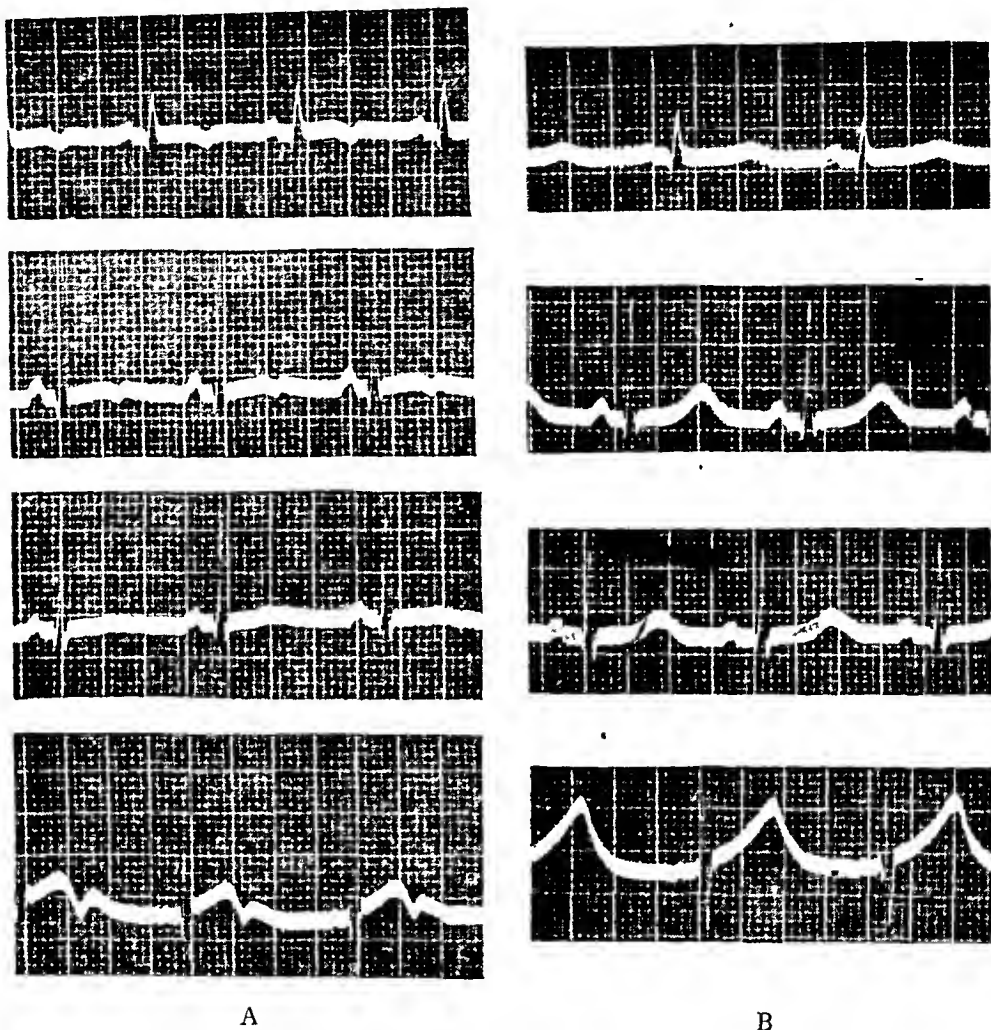


FIG. 2. A. Electrocardiographic tracing taken three days after attack of severe paroxysmal hypertension. B. Electrocardiographic tracing taken 11 days after attack.

A flat abdominal plate and an intravenous pyelogram were normal, there being no evidence of displacement of the kidneys. A perirenal air insufflation under fluoroscopic control outlined a normal right adrenal gland. Two days later, however, the introduction of 120 c.c. of air in the region of the left kidney "shows the left kidney to be well seen and outlined by air in the capsule. Lying over the upper pole and within the capsule is a rounded smooth-edged mass measuring 9 by 7.5 by 6 cm. This mass lies anteriorly to the upper pole of the kidney and causes slight compression of the upper pole. The findings are those of a tumor of the left adrenal, probably a pheochromocytoma" * (figures 4 and 5).

* The roentgenological observations were interpreted by Lt. Col. James R. Lingley, M.C., and Captain S. M. Wyman, M.C.

Because of the marked response in blood pressure to 0.5 mg. of histamine, we attempted to determine the degree of sensitivity of this patient to small doses of the drug. The following study (figure 6) was made:

Histamine phosphate in doses of 0.01 mg., 0.02 mg. and 0.06 mg. was administered intradermally after a normal base line of blood pressure had been reached. The second injection was made five minutes after the first, the third being given eleven and one half minutes after the first. Fifteen minutes after the original injection, the symptoms of a hypertensive paroxysm were noted. The blood pressure began to rise reaching its peak of 290 mm. systolic 22 minutes after the initial dose. At this point the patient's symptoms and signs were maximal. It is interesting to note that there followed a secondary asymptomatic paroxysm of 260 mm. systolic after the pressure was falling back towards normal (35 minutes after the start of the test). From these studies the value of histamine phosphate as a diagnostic test seemed apparent. However, the resulting response was quite alarming even though only .09 mg. was injected.

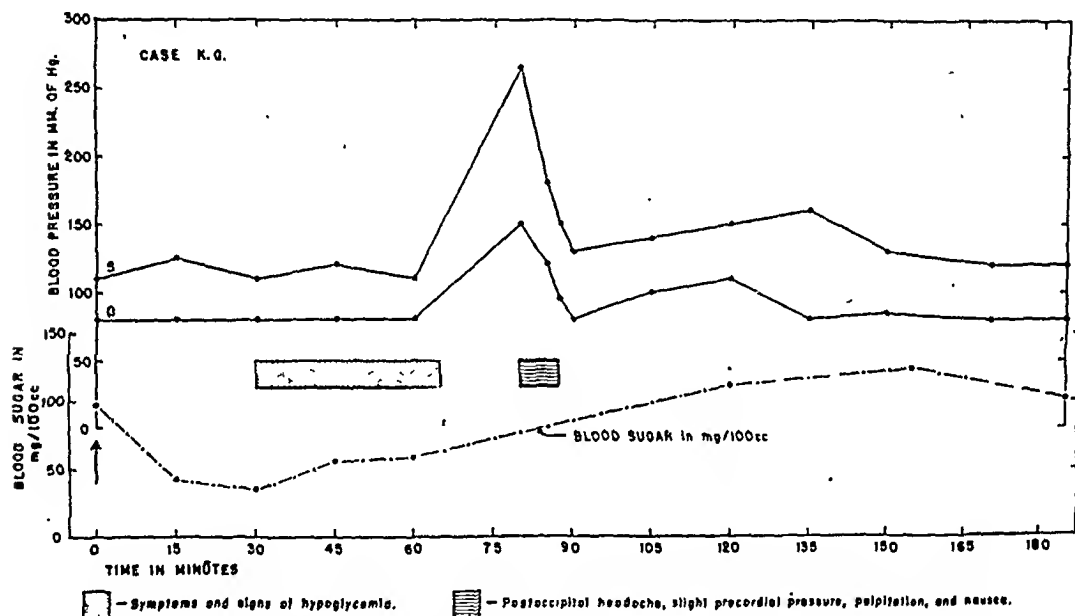


FIG. 3. Blood pressure and blood sugar response following intravenous injection of four units of crystalline insulin.

The patient was transferred by air to the Walter Reed General Hospital for surgical operation on July 11, 1943. On August 10, 1943, under spinal anesthesia, Lt. Col. Lloyd G. Lewis, M.C., of the Urology Service, operated on the patient, removing the adrenal tumor and the left adrenal gland by the technic described in his operative note as follows:

"An S-shaped incision was made from the base of the twelfth left rib running anteriorly and then downward at the border of the rectus muscle. The abdominal muscles were then divided. The peritoneum was retracted medially to expose the perirenal fascia. The twelfth rib was resected. The perirenal fascia was incised and the upper pole of the left kidney was exposed. By retraction of the kidney downward the adrenal was pulled into the wound and sufficiently exposed. The tumor measured 7 by 6 cm. The blood supply from the diaphragm was isolated and divided. As pressure was made over the tumor the blood pressure would be alarmingly elevated as shown in the graphic chart (figure 7). The blood supply from the upper pole of the

CASE REPORTS



• FIG. 4. Antero-posterior view of left kidney area after perirenal air insufflation, showing tumor mass.
FIG. 5. Left lateral view of the left kidney area, after perirenal air insufflation, showing tumor mass.

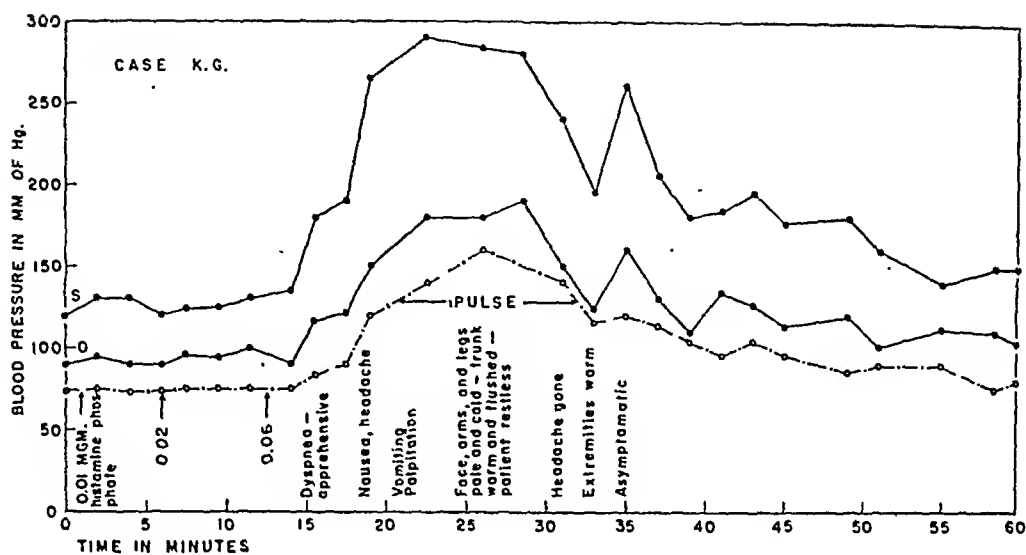


FIG. 6. Blood pressure response to intradermal injection of 0.01 mg., 0.20 mg. and 0.06 mg. of histamine phosphate before operation.

left kidney was then isolated and divided. When the tumor was elevated to expose the adrenal pedicle on the posterior surface of the tumor, the blood pressure became elevated to 274 mm. Hg. Traction on the pedicle was relieved to allow the pressure to return to normal levels. When a Kelly clamp was placed on the large artery, the pressure suddenly fell to 65 mm. Hg. The clamp was then removed to allow the blood pressure to return to normal by the expression of adrenaline into the circulation from the tumor. The pedicle was then doubly clamped, divided, and ligated. Practically all of the left adrenal was involved in the tumor and was also removed. The wound was then closed and the patient was returned to his ward in good condition. During the operation he was given continuous intravenous infusions of plasma and glucose and,

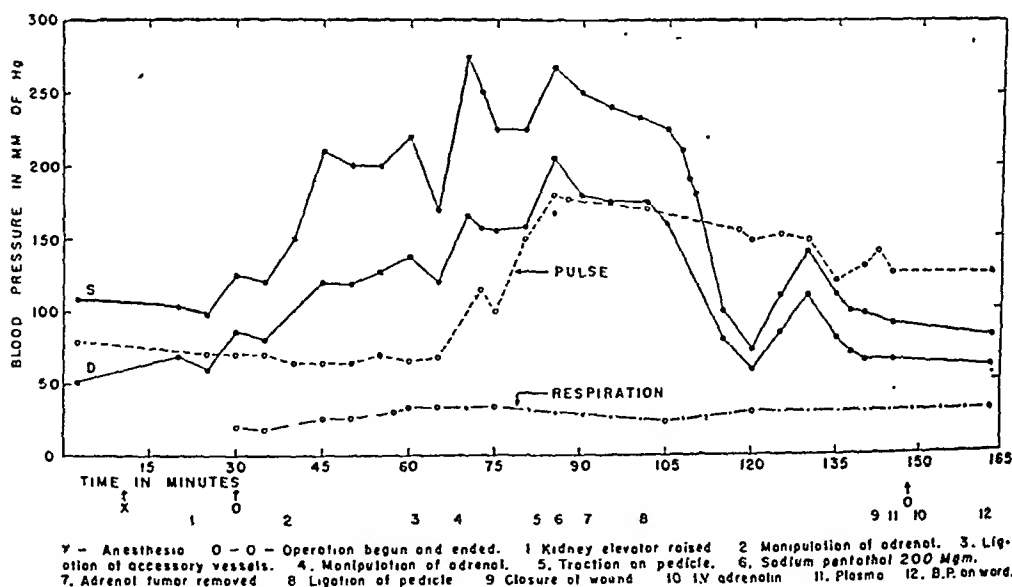


FIG. 7. Anesthesia record during excision of the tumor of the left adrenal gland. Case K. G., Walter Reed General Hospital, August 10, 1943.

when needed, a few minims of epinephrine. For the first 36 hours after operation he was given ephedrine in oil and adrenal cortical extract every four hours intramuscularly."

The patient recovered uneventfully from the operation, being discharged from the Army on October 20, 1943. At this time he was completely asymptomatic and his ulcer was quiescent. His basal blood pressure level remained at 95 systolic and 65 diastolic and there were no more symptoms of hypertensive paroxysms. A repeated histamine test and insulin tolerance test failed to produce an elevation of blood pressure.

The pathological examination of the tumor was made at the Army Medical Museum which has furnished photographs of the pathological specimen and photomicrographs of the sections (figure 8). A diagnosis of benign pheochromocytoma was

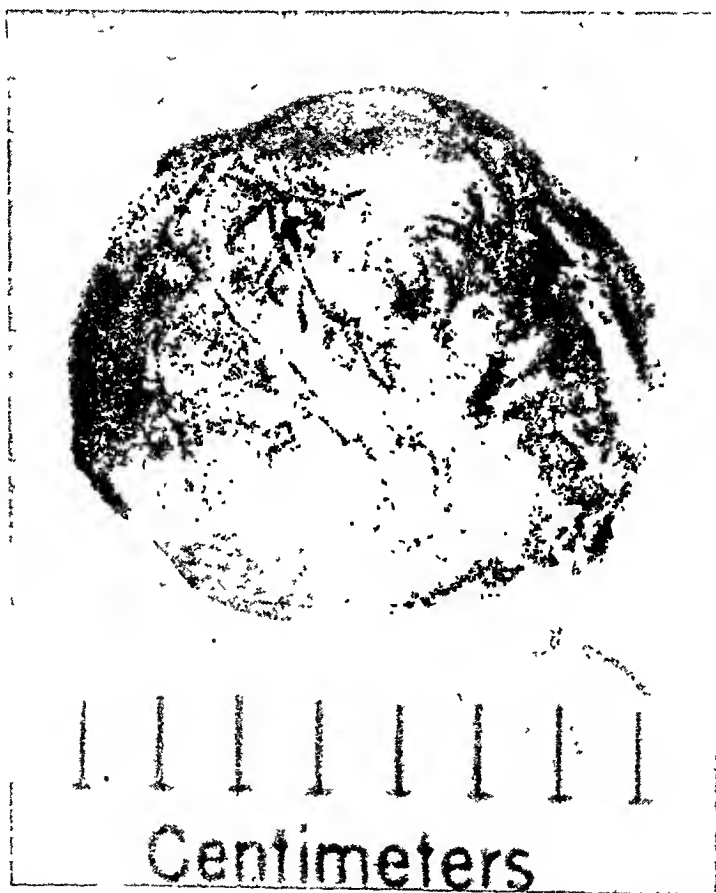


FIG. 8. Gross specimen of the tumor, benign pheochromocytoma of the left adrenal gland. (Courtesy of Army Medical Museum.)

made. There was no assay of adrenaline content or pressor substance made in this case.

DISCUSSION

The value of histamine phosphate as a helpful test in the diagnosis of pheochromocytoma which has been previously described by Hyman and Mencher⁷ and Roth and Kvale,²⁰ was confirmed in this case. Best and Taylor²⁶ state that there is some evidence that histamine increases the output of adrenaline from the adrenal medulla. Weiss, Robb, and Ellis²⁷ found that, whereas the

subcutaneous administration of histamine phosphate in pharmacologic doses resulted in a momentary depression of the systolic blood pressure due to generalized vasodilatation, the continuous intravenous infusion of histamine failed to show any appreciable variation of the systolic pressure. This fact they attribute to two factors: (a) the rapid destruction of histamine in the body and (b) the stimulation of effective compensatory cardiovascular reflexes which act through sympathetic cardio-acceleration, vasoconstriction, and the discharge of adrenaline. Thus it would appear that the histamine test produces a compensatory discharge of adrenaline.

Although in man the adrenaline store of both normal adrenals is about 10 milligrams,²⁶ assays of adrenaline content of individual pheochromocytomas have been reported as high as 682 milligrams.¹⁸ Thus the exaggerated response to histamine in cases of pheochromocytoma would seem to be due to the additional adrenaline available from the tumor. It would appear, however, that the production of a paroxysm of hypertension as seen in figure 6 resulting from the injection of histamine is not without considerable danger as shown by the electrocardiographic changes in this case and the extreme height of blood pressure resulting. Such a blood pressure response might result in rupture of a cerebral blood vessel, produce pulmonary edema or shock. Higglan and Holzmänn, as mentioned by MacKeith,¹⁵ describe similar electrocardiographic changes, particularly inversion of the T-waves after a spontaneous attack in a case of pheochromocytoma. Palmer and Castleman²⁸ report a case of pheochromocytoma in which paroxysms were noted following intravenous medication, and in which sudden death occurred during an intravenous infusion of 10 per cent glucose solution.

The specificity of the test has been well shown by Roth and Kvale¹⁸ who report its diagnostic significance in three cases of proved pheochromocytoma, whereas their controls, a group of normal persons, a hyperreactor group, and a group of established hypertensive patients, showed only minor responses in blood pressure, after the injection of histamine phosphate. In the control groups the average maximum increase of systolic pressure was 36 mm. of mercury. In the three cases of pheochromocytoma a rise of the magnitude of 100 mm. or more of mercury in systolic pressure occurred. After operation with the successful removal of the tumor in their cases, no rise in blood pressure or symptoms could be elicited after the use of histamine phosphate. This was likewise true in our case.

In addition to the use of histamine phosphate, adrenaline and insulin have also been found to produce a hypertensive reaction in cases of pheochromocytoma.⁷ The cold pressor test may or may not produce a paroxysm in such cases. Emotional reactions such as fear, anger, or pain, and physical changes such as exertion, mild trauma, changes of posture (lying to sitting position), hyperventilation, massage over the tumor, or pressure produced by lying on the affected side, have been shown to cause an abnormal response in the blood pressure. In our patient it is of interest that such influences, even including parachute jumps, did not result in symptoms.

The symptomatology appears to be the result of discharge of either adrenaline or an adrenaline-like substance into the general circulation from these tumors.⁷ The presence of such a pressor substance was first demonstrated by Beer, King,

and Prinzmetal²¹ and confirmed by Hyman and Mencher.⁷ The symptomatology produced during the attacks, whether spontaneous or induced, is more or less similar, differing only in the degree of severity of the response. Such symptoms as recurrent attacks of severe pulsating headaches, dyspnea, palpitation, orthopnea, sweating, vomiting, abdominal cramps with blanching of the face and extremities should suggest this syndrome. These attacks may last for minutes to hours⁷ or may result in a state of shock which may prove fatal.

The state of shock which follows in the latter cases seems probably dependent on the massive and prolonged introduction of adrenaline into the general circulation.⁷ A similar condition has been shown to obtain in experimental animals by Freeman, Freedman, and Miller²⁴ who observed the appearance of a shock-like state in dogs after a continuous intravenous infusion of adrenaline over a period of one to one and a half hours. They interpret this state as being due to a marked reduction of the circulating blood volume. They believe that when adrenaline was discontinued, the arterioles then dilated, and caused a fall in blood pressure with anoxia of the vital centers. A reflex vasoconstriction in the presence of a diminished blood volume was ineffective to maintain the animal's life. It is thought that the state of shock which often occurs following the removal of these tumors may be due either to the above sequence of events with reduced blood volume, or to the ineffectiveness of the normal amount of circulating adrenaline to maintain the blood pressure by its action on arterioles accustomed to large amounts of circulating adrenaline from the functioning tumor. A third factor may be a lack of circulating adrenaline due to atrophy of disuse in the normal adrenal medulla which perhaps may occur in the presence of the production of excess adrenaline from the tumor. This is the rationale for the use of pressor substances such as adrenaline and ephedrine postoperatively.

Furthermore associated with potential absence or atrophy of the opposite adrenal gland a temporary adrenocortical insufficiency may result when the involved gland is removed. Biskind et al.⁴ recommend the use of adrenal cortical extract and Hyman and Mencher⁷ suggest the additional use of desoxycorticosterone acetate and salt both preoperatively and postoperatively in such cases. Additional evidence for its use is found in the report of Perkins, Swingle, Taylor, and Hayes²⁵ who have shown that the administration of adrenal cortical extract is of aid when the circulatory collapse of adrenaline-produced shock obtains. When salt and desoxycorticosterone acetate are used both preoperatively and postoperatively overdosage must be guarded against since serious pulmonary and myocardial edema may intervene.

An elevated basal metabolic rate and diabetic type sugar tolerance curves have been noted in some cases of pheochromocytoma. Determinations for these were not made in our case. Duncan, Semans and Howard¹⁴ report a case of their own and nine cases from the literature which showed an association of pheochromocytoma with diabetes mellitus. McCullaugh and Engel²² and Duncan et al. report cases in which there were elevations of the basal metabolic rate ranging from plus 25 to plus 60. Thus since the altered physiology of hyperglycemia, glycosuria, and elevated basal metabolic rates may return to normal levels after operative removal of a pheochromocytoma, Duncan et al. suggest that "when diabetes mellitus, hypermetabolism, and hypertension are encountered together, the possibility of a pheochromocytoma should be considered."

The occurrence of peptic ulcer in this patient with adrenal medullary hyperactivity is worthy of comment as it is unusual for an ulcer to develop in conditions where sympathetic overstimulation occurs, as in hyperthyroidism. There is some evidence that sympathetic stimulation and adrenaline inhibit gastric secretion.²⁰

The localization of the tumor is best achieved by the technic of perirenal air insufflation which was so successfully used in this case.²³ However, a flat abdominal film followed by an intravenous or retrograde pyelogram may suffice. Brunschwig and Humphreys⁵ report the distribution of the tumor in 103 autopsy cases as follows: 43 cases involving the right adrenal gland; 34 cases involving the left; 13 cases with bilateral adrenal involvement; and 13 cases which were outside the adrenal gland. Biskind et al.⁴ confirm the prevalence of involvement of the right adrenal gland, and report the following distribution in their preoperatively diagnosed cases: 18 involving the right, seven involving the left, and four outside either gland. In the few cases in which the hyperfunctioning adrenal medullary substance lies outside the adrenal area, a search must be made along the abdominal aorta, in the carotid body, in the organ of Zuckerkandl, in the retroperitoneal tissues, or in the sacrococcygeal region where other chromaffin tissue may be found. The presence of additional functioning tissue in these areas may explain recurrent symptoms after operative removal of a functioning tumor, as in the case reported by MacKenzie.³⁰

Hypertension which is of the fixed type does not necessarily exclude the possibility of a pheochromocytoma as was demonstrated by the case reported by Thorne et al.¹²

SUMMARY

A case of pheochromocytoma of the left adrenal gland with successful operative removal and recovery is reported.

The previously reported use of histamine phosphate as a diagnostic procedure is confirmed. The use of this substance is attended with potential danger and should be employed with great caution.

The clinical picture and laboratory diagnostic studies are discussed.

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UNUSUAL COMPLICATIONS OF AMEBIASIS *

By BERNARD M. CHAPMAN, *Chicago, Illinois*, HAROLD SCHWARTZ,
and DONALD B. HAISLIP

AMEBIASIS has popularly been considered a disease of the tropics. This, however, has long been known to be incorrect. Ochsner and De Bakey¹ have stated that amebiasis exists in 10 to 20 per cent of the population of the United States. Its incidence in the tropics is, however, very much higher and it was therefore to be expected that our returning troops would bring back the disease to this country and make it of much greater significance to the practicing physician.

Amebiasis is a disease with protean manifestations. The term "amebic dysentery," which describes only one symptom, is inadequate. It is not unusual to find the disease first recognized through some of its complications in the absence of dysentery, history of dysentery, or amebae in the stools. The following is a case report of a patient with amebiasis which demonstrates most unusual complications.

CASE REPORT

History: A 27 year old white soldier was transferred to the Oakland ASF Regional Station Hospital from another Army hospital on May 8, 1946. A complete history was difficult to obtain because of the extremely critical condition of the patient. The story as given was as follows: Approximately on April 12, 1946, two weeks before his hospitalization, the patient began to notice dull right upper quadrant pain. This became gradually worse until he could no longer stand it, and on April 26 he stopped an officer on the streets of Reno, asking for help. He had noticed chills and fever, but thought them to be due to malaria, which he had had before. At the time of his hospitalization he had been on a drinking spree. He had been drinking at least a quart of whiskey and beer every day for several weeks. He had neglected his meals completely. The pain in the right upper quadrant was constant, not cramping, radiating somewhat into the back and up to the right shoulder. He had noticed no changes in his urine or in his stools, and he was not jaundiced. The patient denied any previous history of hepatitis or dysentery. Upon admission to the hospital on April 26, his temperature was 102° F., and the white blood cell count was 20,000. The patient's illness was diagnosed as infectious hepatitis and was treated as such with intravenous fluids. He was also given quinine and plasmoquin because of the possibility of malaria, although no positive smear could be obtained. On May 4, 1946 edema of the ankles was noted and râles were heard in the left lung base. On May 6 for the first time, icterus was noted. The leukocyte count was 19,350. The temperature rose to 104° F., and the patient became lethargic and stuporous. He was given sulfadiazine and penicillin with no improvement. The abdomen became distended, respirations became stertorous, and he did not respond to questioning. He was transferred to our hospital on May 8, 1946 in a critical condition.

Physical Examination on Admission: Temperature 101.4° F., pulse 120, respirations 32. Patient was a poorly nourished, extremely ill, 27 year old white soldier who did not respond coherently to questioning. The skin was moderately icteric; the mucous membranes were extremely dry. The respirations were stertorous and

* Received for publication October 15, 1946.

Credit is given to U. S. Army Air Force, Pacific Overseas Air Technical Service Command, for photographs of gross specimens.

noisy. The heart was not enlarged, the rhythm was regular, and there were no murmurs. The liver was tender. Its dullness was percussed up to the nipple line, and extended four fingers' breadth below the right costal margin. The breath sounds were suppressed at the lung bases, especially at the right, and there were numerous coarse rhonchi throughout both lung fields. The abdomen was distended. There were distended superficial veins in the right upper quadrant. There was three plus pitting edema of the sacrum and lower extremities. The stool was brown and apparently contained bile pigments.

The differential diagnosis at the time of admission lay among hepatitis, liver abscess, and ruptured intra-abdominal viscus with secondary liver abscess.

Laboratory Examination: Urinalysis showed specific gravity 1.016, 1 plus albumin, no sugar, 5 to 10 leukocytes per high-power field, few pus cells, few granular casts. Test for urobilinogen was positive in a dilution of 1 to 40. Blood count revealed 3,300,000 red blood cells, 19,750 white blood cells, with 66 per cent hemoglobin and 80,000 platelets. Smear showed 80 per cent polymorphonuclear leukocytes, 19 per cent lymphocytes, 1 per cent eosinophiles. There were 3 per cent myelocytes. There was marked toxic granulation of the white cells. The blood urea nitrogen was 6.2 mg. per 100 c.c., blood sugar 55 mg. per 100 c.c., chlorides 450 mg. per 100 c.c., cholesterol 133.5 mg. per 100 c.c.; the icterus index was 50. The Van den Bergh showed a direct positive reaction and 2.1 mg. indirect. Stool examinations were negative for amebae and cysts as well as for other parasites. There was bile in the stool. Serum proteins on May 9, 1945 showed 4.9 gm. total protein, 1.9 gm. albumin, 3.0 gm. globulin; giving an A.G. ratio of 0.63. A blood count on May 9, 1945 showed 3,610,000 red blood cells, 66 per cent hemoglobin, 16,200 white blood cells with 94 per cent polymorphonuclears, and 6 per cent lymphocytes. Of the 94 per cent polymorphonuclears 5 were stabs, 3 were metamyelocytes, and 2 were myelocytes.

Treatment and Course: The patient was treated vigorously with intravenous glucose, plasma, and human serum albumin, in order to reestablish electrolyte and protein balance, and with penicillin to combat infection. Roentgen-ray of the chest on May 9, 1946 showed marked elevation of the diaphragm, presumably from an enlarged liver. The heart was displaced slightly to the left. The patient improved somewhat during the next 48 hours. He became coherent and was able to respond to questions. Because of the possibility that the condition might be an amebic hepatitis, emetine was begun. However, he did not improve satisfactorily and it was thought that he should be explored surgically. The temperature ranged between 99 and 103° F., and was septic in type. A repeat chest film on May 11, 1946 showed an increase in the elevation of the right diaphragm with haziness just above it. The liver edge was thought to extend below the iliac crest. The radiologist believed the findings to indicate a mass in the liver, presumably inflammatory. The patient was therefore taken to the operating room where a sub-costal incision was made and an enlarged liver was found. An aspirating needle was inserted into the liver and frank pus was obtained. The wound was packed in order that adhesions should form and thereby allow drainage at a subsequent procedure. The patient withstood the procedure well and was returned to the ward. Direct smear of the aspirated material showed granular debris, degenerated cells, and no organisms. Culture of this material was sterile. On the following day an abscess cavity was opened by cauterization. About 200 c.c. of brownish gray material was aspirated. At the time, it was thought that there must be multiple abscesses, because a solitary abscess with only 200 c.c. did not appear to explain the clinical picture. Treatment was continued with intravenous fluids, plasma, vitamins, emetine, and penicillin. On May 10, 1946 the nonprotein nitrogen had been 70 mg. per cent and the blood urea nitrogen 28 mg. per cent, but on May 13 the nonprotein nitrogen had risen to 120 mg. per cent, and the blood urea nitrogen to 50 mg. per cent. The white count at this time was 10,500,

and the hemoglobin was 75 per cent. The icterus index had risen to 100. The patient became progressively more and more edematous. He died at 0810 hours May 16, 1946.

Autopsy Report: Body is that of a thin, poorly nourished, white male about 27 years of age, measuring 72 inches in length, and weighing approximately 120 pounds. The skin and conjunctivae are icteric. In the right upper quadrant parallel to the costal margin there is a recent, 15 cm., surgical incision that has been left open and gaping. There is marked pitting edema of the legs, feet and scrotum. On opening the abdominal cavity the omentum is found to be adherent to the liver and plastered beneath the incision. The parietal peritoneum around the incision is adherent to the liver. At about the anterior axillary line at the costal margin there is a recent incision in the liver, which leads into an abscess cavity, which measures about 5 cm. in diameter, and still contains some thick viscid material.

After dissecting the anterior abdominal wall away from the mass in the epigastrium, it is found that this mass consists of an abscess which contains thick mucoid material. The boundaries of the abscess are: superiorly, the liver; anteriorly, portion of the liver, the omentum, and the anterior abdominal wall; medially, the gall-bladder and the first portion of the duodenum; inferiorly, the first portion of the duodenum and transverse colon; and posteriorly, the right kidney, right adrenal, and posterior abdominal wall. After aspirating the contents of the abscess it is found that there is a perforation in the duodenum, 1 cm. in diameter, the lumen of which is in communication with the abscess. There is also a perforation measuring 3 mm. in diameter in the fundus of the gall-bladder which communicates with this epigastric abscess.

Liver: The liver is tremendously enlarged, weighing 4,900 gm. The right half of the liver is the seat of multiple liver abscesses, the largest measuring 15 cm. in diameter (figure 1). The liver pushes the diaphragm up to the second interspace on the right side, but there apparently is no involvement or perforation through it. The walls of these abscesses are ragged, shaggy, and several communicate with adjacent abscesses. In the left half of the liver there are smaller scattered abscesses measuring up to 0.5 cm. in diameter. The contents of the abscesses are composed of the same thick mucoid material; in some this material is chocolate in color, in others it is grayish tan.

Pleural Cavities: The left pleural cavity contains focal fibrous adhesions posteriorly and anteriorly, and contains a few c.c. of cloudy amber fluid. The right pleural cavity contains about 1,500 c.c. of a cloudy amber fluid. There are focal fibrous adhesions to the lower lobe posteriorly. There are no inflammatory adhesions or fistulations between the diaphragm and the inferior surface of the right lower lobe of the lung. The pleural surface of the right diaphragm is smooth and shiny. The diaphragm on the left is at the level of the fifth rib; on the right it is at the level of the second interspace.

Lungs: The right lung weighs 650 gm. All three lobes are subcrepitant. The pleural surfaces are irregularly nodular. The entire lower lobe and lower portion of the upper lobe contain nodules up to 1 cm. in diameter which on section are areas of consolidation, some of which are undergoing degeneration and central softening. The lung tissue between these areas is dark greenish brown and firm. There are large areas of fibrin exudate on the pleural surface of the right lower lobe posteriorly. The larger branches of the bronchi are clear. The larger branches of the pulmonary artery are also clear.

The left lung weighs 520 gm. The apex of the upper lobe is emphysematous. The lower portion of the upper lobe contains nodules, up to 1 cm. in diameter, as described above. The lower lobe also contains focal areas of consolidation, and early abscess formation. The large bronchi and larger branches of the pulmonary artery are clear.

Kidneys: The kidneys together weigh 650 gm. They are firm and appear somewhat swollen. The anterior and superior surface of the right kidney is covered with shaggy necrotic material that replaces a portion of the cortex. This is apparently secondary to the overlying epigastric abscess. For an area of 8 cm. in diameter



FIG. 1. Coronal section through liver showing multiple liver abscesses.

there is involvement of the cortex up to 1 cm. in depth. In this area there are multiple small abscesses composed of necrotic material. The right adrenal gland is markedly hemorrhagic and is also involved in the necrotic process. The left kidney is swollen. The kidneys are somewhat icteric, the markings indistinct, and the average cortical thickness is 7 mm.

Colon: The large bowel shows some millet-seed sized areas of ulceration beginning at the level of the splenic flexure. These become more numerous and larger in the ascending colon and cecum. These ulcers present dark red overhanging edges, and a gray necrotic base. The ulcerations in the ascending colon and cecum are characterized by a gangrenous margin with overlying edges and a yellowish-gray necrotic base (figure 2). Some of these ulcerations are confluent. There is no evi-

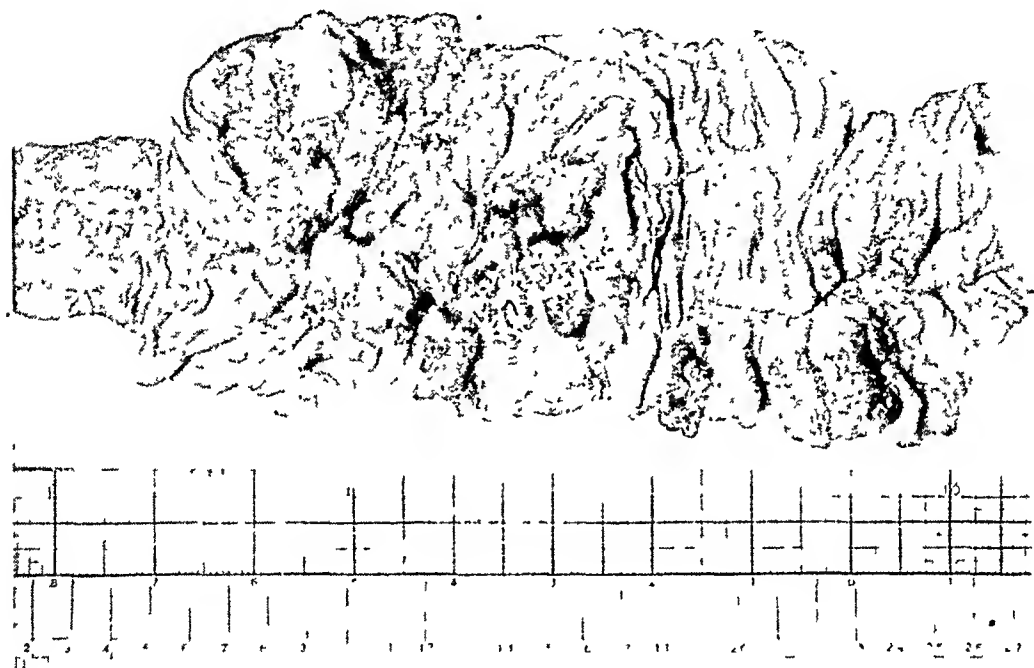


FIG. 2. Cecum and ascending colon: typical necrotic amebic ulcerations (Note normal mucous membrane between ulcerations)

dence of perforation and no ulcer extends deeper than the muscularis of the bowel. The mucous membrane between the ulcerations is perfectly normal or only slightly edematous. The terminal portion of the ileum shows moderate congestion and edema of the mucosa but the ulcerations end sharply at the ileocecal valve

Spleen: The spleen shows evidence of hyperplasia and congestion

Heart: The heart is small and flabby.

Prostate, bladder, pancreas, thoracic and abdominal aorta and brain are essentially normal.

Smears from the ulcerations in the bowel showed actively motile amebae typical of *Entamoeba histolytica*.

Microscopic Description: Cecum and Ascending Colon: Sections of ulcers in cecum and ascending colon reveal the edge of the overhanging mucosal margin of the ulcer to be gangrenous. This gradually blends into normal appearing mucosa. This mucosa covers an area of colliquative necrosis in the submucosa, which consists of a mass of degenerated tissue cells, debris, and an occasional round cell. Trophozoites are abundant in the necrotic debris and more especially in the growing margin of the ulcer. Figure 3 shows a high power magnification of the wall of the

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colon with numerous amebae growing in the submucosa. Throughout the sections amebae can be seen lying free in the lymphatic spaces and small venules. In the center of the ulceration the necrosis extends down to but does not involve the muscularis of the bowel.

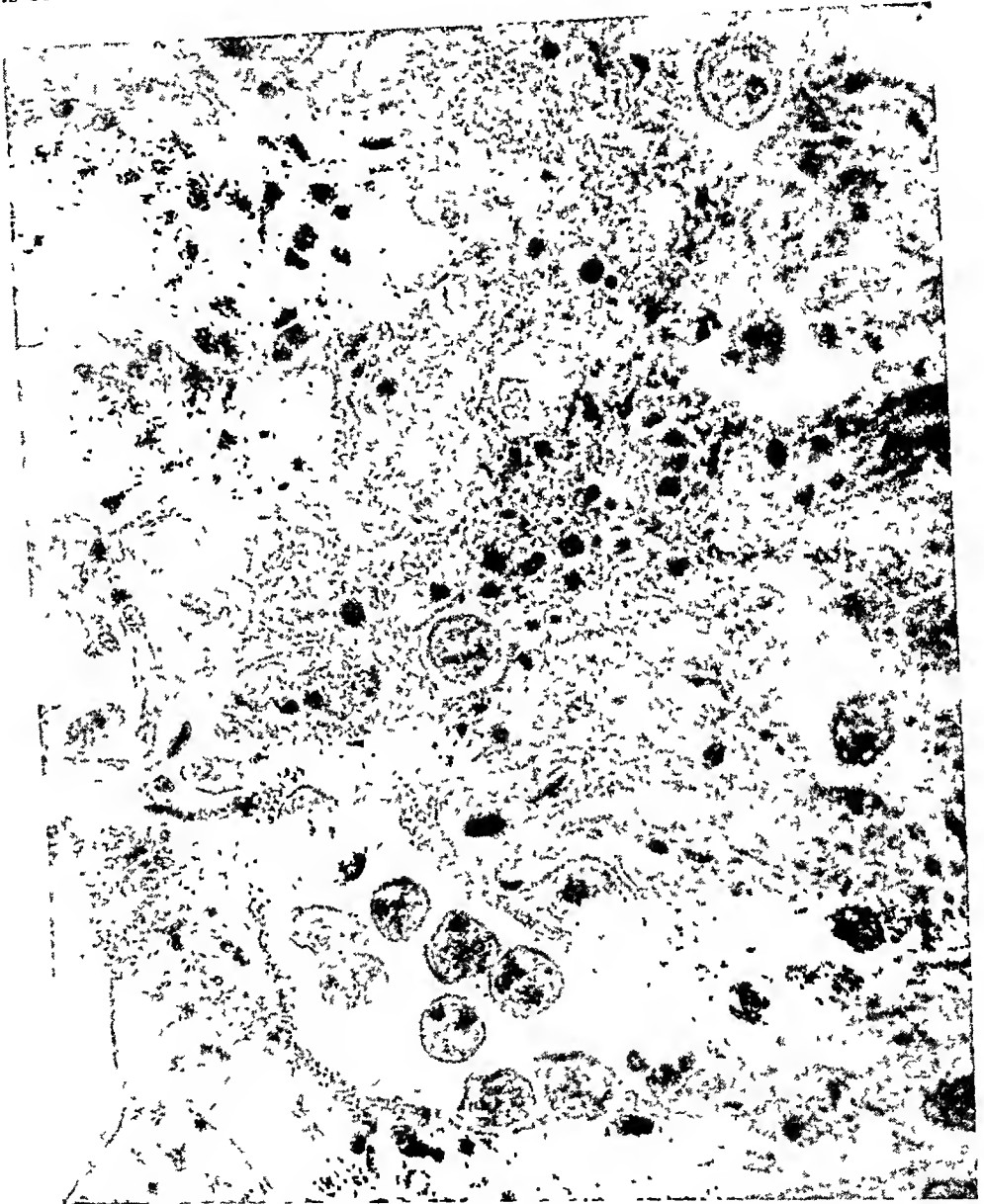


FIG 3. Section through margin of ulcer in ascending colon, magnification $\times 500$. Typical amebae are seen in the wall of the bowel, and are grouped in colonies. The submucosa is edematous and is sparsely infiltrated with round cells. The clear spaces surrounding the amebae are due to proteolytic digestion.

Liver: Sections of liver through the wall of the abscess (figure 4) show relatively little fibrous tissue reaction indicating the recent duration of the lesion. Fewer amebae are seen in the wall of the abscesses than in the sections of intestine or lung. The intervening liver tissue shows evidence of parenchymatous degeneration. Many of the bile canaliculi are plugged with inspissated bile. The periportal spaces show

an increase in fibrous tissue, and in places marked round cell infiltration. The abscesses vary in size from the large abscesses mentioned in the gross description to innumerable abscesses of microscopic size. The sections taken from grossly normal



FIG. 4. Section through liver abscess showing liver tissue infiltrated with round cells and an occasional ameba. Margin of liver abscess shows proteolytic dissolution of liver cells and beneath this there is granular debris which is the result of the colliquative necrosis. Arrows point to amebae in the granular debris of the abscess and in the growing margin. (Photomicrograph $\times 120$ H & E.)

liver also show lesions microscopically. In many sections there are small abscesses beneath the capsule of the liver. In some of the abscesses there is hemorrhagic extravasation. Many of the abscesses are conglomerate, and communicate with one another. In none is there evidence of secondary infection or suppuration.

Kidney: Sections of the right kidney forming the posterior wall of the epigastric abscess, show marked destruction of the cortex. Practically the entire cortex is replaced by shaggy necrotic material that extends well into the medulla. In some sections the connective tissue skeleton of the glomeruli and tubules are still visible,

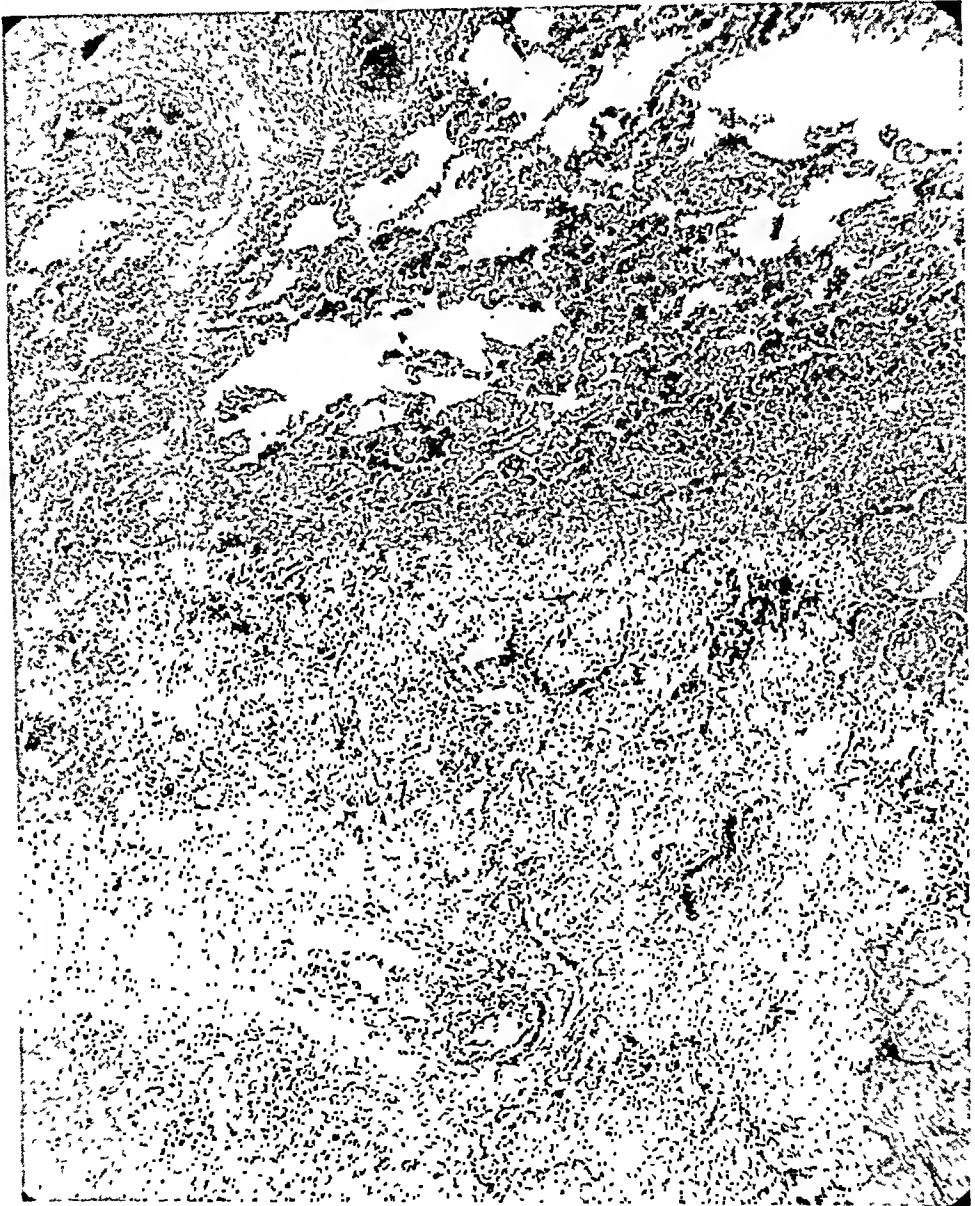


FIG. 5. Section through margin of nodule in lung, showing thickened alveolar septa and some atelectasis. This surrounds the area of consolidation to the right. The alveoli are filled with necrotic granular debris. The alveolar septa are fairly well preserved. (Photomicrograph $\times 50$ H & E.)

but the epithelial elements are digested. There are large collections of colliquative necrosis and granular debris as seen in the liver sections. In this debris, and out to the margins of uninvolved kidney, are seen numerous trophozoites. The kidney parenchyma at the margins of this necrosis shows moderate interstitial round cell infiltration. The glomeruli are swollen and somewhat more cellular than normal.

The convoluted tubules are the seat of moderate to severe albuminous degeneration, and some of the collecting tubules show casts of granular debris and an occasional hemoglobin cast. Sections through the left kidney show normal glomeruli, mild albuminous degeneration of the convoluted tubules and an occasional granular cast in the collecting tubules. The renal pelvis and ureter are normal.

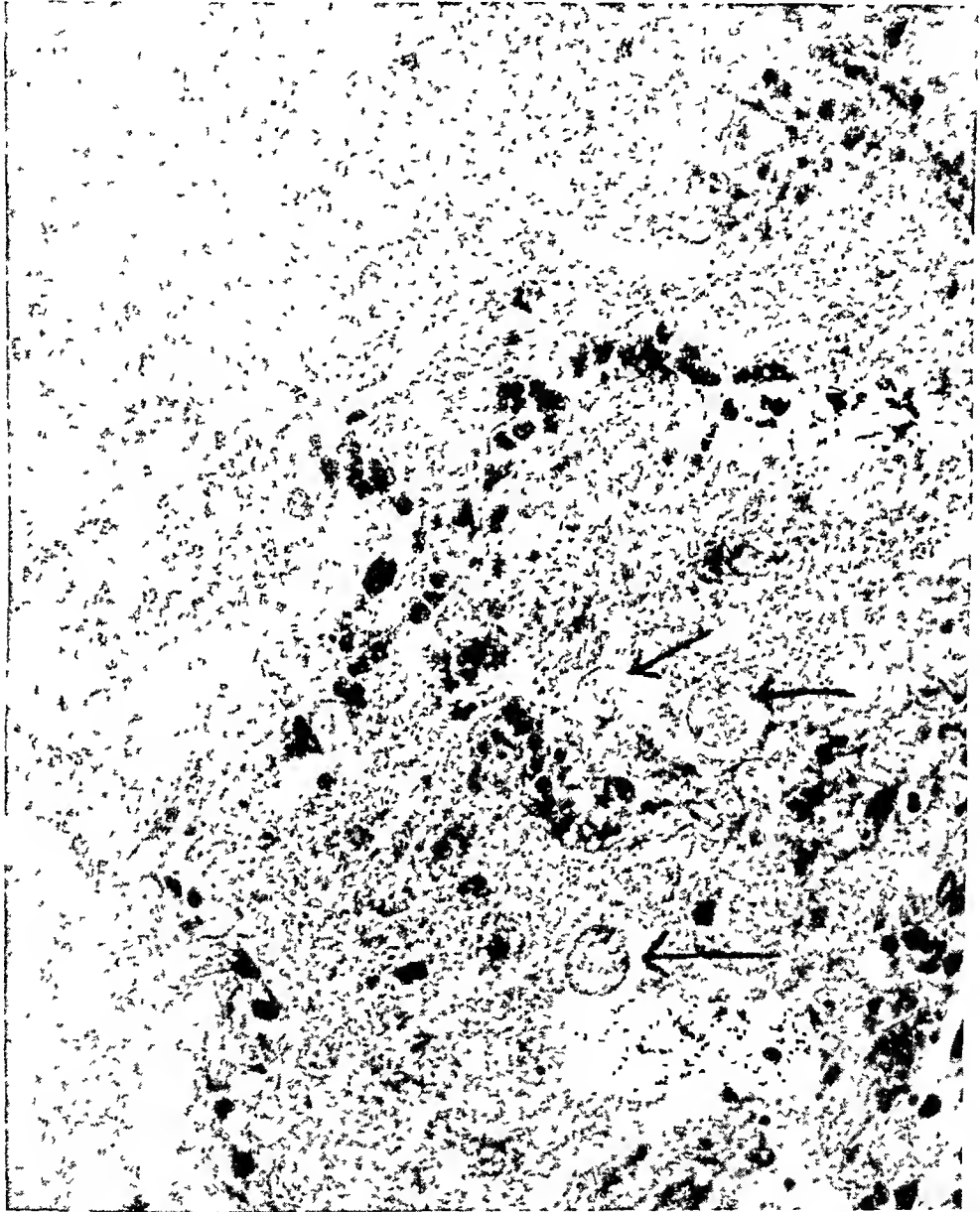


FIG. 6. Section through center of consolidation seen in figure 5. Magnification $\times 500$. Alveoli are filled with granular debris and amebae. Alveolar septa are fairly well preserved. There is no inflammatory reaction. Arrows point to amebae in alveoli.

Lungs: Sections through the nodules in the right lower, left lower, and left upper lobes show a similar picture. There is a peculiar type of pneumonitis in which the alveoli in the center of the nodules are filled with necrotic material and granular debris (figure 5). There are numerous trophozoites found lying free in the alveoli among the granular debris (figure 6). Some of the alveolar septa are destroyed but

for the most part they are fairly well preserved. Around the circumscribed abscesses there are alveoli with thickened septa and focal areas of atelectasis. There are numerous macrophages filled with blood pigment and debris in the alveoli around the nodules. In some sections trophozoites can be seen in the small vessels between the alveolar septa. Sections through the pleura of the right lower lobe show marked thickening with some necrosis and amebae lying in the pleural wall. The bronchi are distended and filled with necrotic debris. Numerous amebae can be seen in the lumen of the bronchi.

Heart: Sections of heart show evidence of mild parenchymatous degeneration.

Bone Marrow: Sections of bone marrow reveal a depression of hematopoiesis.

Adrenal Gland: The right adrenal adjacent to the epigastric abscess shows colliquative necrosis with numerous amebae. The left adrenal is normal.

Duodenum: Section through the margin of the perforation in the duodenum shows marked edema with necrosis of the margin. Amebae are found in the mucosal folds and in the submucosa.

The pancreas, spleen, urinary bladder and brain are histologically normal.

Anatomical Diagnoses: Amebiasis: multiple amebic ulcerations of the large intestine; multiple amebic liver abscesses; perforation of liver abscess with formation of epigastric abscess; perforation of epigastric abscess into duodenum; small focal amebic abscesses of right upper and lower, and left upper and lower lobes of the lung.

COMMENT

Summarizing, we have presented here a case of amebiasis with multiple liver abscesses, one of which ruptured intraperitoneally and subsequently into the duodenum; multiple, focal amebic abscesses of both lungs without diaphragmatic involvement; and classical amebic ulceration of the colon, without demonstrable amebae in the stools. Each of the complications found has been previously described in the literature, but the combination of all in one patient has rarely, if ever, been reported.

Amebic abscess of the liver has long been known to be one of the most frequent complications of amebic dysentery. Ochsner and De Bakey¹ report 160 cases of amebic abscess of the liver in 1,333 cases of amebic dysentery studied at the Charity Hospital in New Orleans, giving an incidence of 17.4 per cent. Fitcher² in 1903 reported 27 cases of amebic liver abscess in 119 cases of amebic dysentery, giving an incidence of 22.2 per cent. It is interesting to note that immunity to the infection may apparently be developed. Thus, Buchanan³ in 1899 found that the ratio of amebic liver abscesses to amebic dysentery in India among natives was one to 628, while among the Europeans it was one to 18. Whereas the amebic liver abscess is commonly thought to be solitary, review of autopsied material indicates that this is only partially true. In Ochsner and De Bakey's¹ clinical series of 140 cases, 88.6 per cent were solitary and 11.3 per cent multiple. The incidence of single or multiple liver abscesses depends upon whether clinical or autopsy material is considered. Thus, in a clinical review by Davidson⁴ 75 per cent of cases had single abscesses. Ochsner and De Bakey's¹ review of autopsy material in the literature revealed 60 to 65 per cent multiple liver abscesses in contrast to the 11.3 per cent in their clinical series. However, it must be remembered that autopsied cases of amebiasis are more likely to have had extensive involvement. The mortality of multiple liver abscesses is considered by these investigators to be 100 per cent, while that of solitary abscesses is only 10.5 per cent.

Perforation of amebic liver abscess is not uncommon. It may perforate into the peritoneal, pleural, or pericardial cavities, through the skin or into adjacent viscera. In the case presented, an epigastric abscess developed from the perforation of an amebic abscess on the inferior surface of the liver. This subsequently ruptured into the duodenum. Rupture, in fact, may be the first evidence that a liver abscess exists.⁵

Anderson, Johnstone and Hansen⁶ state that pulmonary abscesses are found in 3 per cent of autopsied cases of amebiasis. They believe that the liver is the main primary focus, and that the extension is via the lymphatics of the diaphragm. Cantlie,⁷ however, directs attention to the possible embolic origin of some amebic lung abscesses. In our case, the latter hypothesis seems plausible, because of the multiplicity of the abscesses and the wide-spread distribution throughout all the lobes of the lung. Furthermore, trophozoites were actually seen in the small vessels between the alveolar septa.

Obviously, amebic infection of the colon always antedates the liver and other metastatic lesions. It is common clinical experience, however, to be confronted with a liver abscess in which no previous history of diarrhea or gastrointestinal symptoms can be elicited. Ochsner and De Bakey,¹ in a review of 966 cases in the literature, have found that only 561 or 58 per cent gave a positive history of antecedent diarrhea. Furthermore, the presence of *E. histolytica* in the stools is not a constant finding. In a collected series of 4,091 cases of amebiasis, *E. histolytica* was found in 474, or 11.6 per cent.¹ The presence of the trophozoite or cyst in the stool is mainly dependent upon the location of the intestinal lesions. When the lesions are in the right side of the colon, diarrhea usually does not exist because there has been no interference with the absorbing power of the bowel. The parasites are less likely to survive in a formed stool than in a diarrheal stool. In lesions of the left side of the colon, impairment of the absorptive power of the bowel is more likely, diarrhea is more frequent, and the parasite is found in a higher percentage of cases. Faust,⁸ Rogers,⁹ and James¹⁰ found lesions in the cecum, appendix, and ascending colon to be the most frequent. This would therefore explain the relative scarcity of amebae in the stools.

SUMMARY

1. A case of amebiasis with unusual complications has been presented.
2. The protean manifestations of these complications is emphasized.
3. The pathogenesis of the metastatic lesions is discussed. The hematogenous mode of spread is suggested in this case by the presence of trophozoites in the small vessels about the lesions in the lung.

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THE OCCURRENCE OF EDEMA OF THE PHARYNX AND LARYNX IN INFECTIOUS MONONUCLEOSIS *

By PAOLO RAVENNA, M.D., *Chicago, Illinois*, and JEROME SNYDER, M.D.,
Baltimore, Maryland

THE symptoms and signs of infectious mononucleosis are variable and imitative of many common diseases. The diagnosis is made by the laboratory findings of a lymphocytosis with atypical cells and of an increased titer of the heterophile antibody (Paul-Bunnell test). Often these tests should be repeated, for a single negative result does not rule out the presence of the disease. Infectious mononucleosis should be suspected in every case of sore throat and in every acute illness with lymph node enlargement and/or splenomegaly, but unfortunately no single physical sign is so characteristic that its finding invites the repetition of the diagnostic tests. Therefore a considerable number of cases remain undiagnosed.

While engaged in the diagnosis and treatment of a large number of young adults suffering from acute infectious diseases in an evacuation hospital of the U. S. Army, we noticed that a certain type of edema of the pharynx was highly suggestive of infectious mononucleosis. One of the patients in this group developed severe edema of the larynx with respiratory obstruction. Such a complication is of interest because it has been stated that laryngeal obstruction is unknown in infectious mononucleosis.¹

The subject of the present note is the description of the pharyngeal edema, a common sign which is useful in the presumptive clinical diagnosis of infectious mononucleosis; and the report of a case of edema of the larynx causing obstruction, a rare and hitherto undescribed complication of this disease.

I. THE PHARYNGITIS OF INFECTIOUS MONONUCLEOSIS

In more than one-half of the cases observed, the pharynx was a brilliant red color, which extended over the arches, the soft palate and the uvula. There was a slight to severe edema of all the oral mucosae, which was most evident in

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the soft palate and the uvula. The uvula acquired a characteristic semitranslucency and at times it was so edematous that it resembled a pear-shaped bag filled with water. Most frequently there was no exudate whatsoever, but at times a slight follicular exudate was seen. The bright red color and the degree of translucent edema, the involvement of the soft palate and the uvula, the paucity or absence of gross exudate characterized this type of inflammation of the pharynx. Often there was sore throat or tickling of the throat, but not rarely in the presence of severe edema the patient denied having the slightest pain in the throat.

In the remaining cases many other types of pharyngitis were frequently seen, but not so commonly as the above described edema. Thus the typical picture of follicular tonsillitis was seen or, more rarely, a unilateral or bilateral ulceration of the tonsil, as in typical Vincent's infection. Vincent's spirilli and fusiform bacilli could be demonstrated in great number in the exudate covering the ulcer. Occasionally a membranous exudate, unilateral or bilateral, was found, which simulated diphtheria, but rarely extended beyond the tonsils.

One of our cases, a young man, was admitted to the hospital with high fever, severe dysphagia and "bullneck"; he had a thick membranous exudate covering both tonsils, so similar to the diphtheritic pseudomembrane that diphtheria antitoxin was administered immediately without waiting for the laboratory reports. The antitoxin had no effect on the fever or the exudate, and later the laboratory reports confirmed the diagnosis of infectious mononucleosis.

Normally when the patients were first seen, enlargement of the lymph nodes of the neck or in other sites was already present, accompanied or not by splenic enlargement. In other cases lymphadenopathy appeared later, but its extension and size were highly variable. Not rarely the swelling of the neck was out of proportion to the size of the cervical glands, and this appeared to be due to inflammatory edema. The general shape and size of the neck sometimes imitated closely the "bullneck" of diphtheria, but the consistency of the swollen neck was always elastic and not so hard as in diphtheria. This swelling caused pain, varying from very slight to severe, but the pain bore no direct relation to the degree of swelling.

The edematous inflammation of the throat lasted for several days, but it did not follow strictly the temperature curve; sometimes it persisted after the patient had been afebrile for several days. In other cases it subsided and became again conspicuous a few days later.

In the frequent instances in which infectious mononucleosis imitated an ordinary follicular tonsillitis, sulfa drugs and penicillin had no effect on its course; in other cases, an apparently typical Vincent's tonsillitis failed to respond to penicillin within one or two days. The lack of response to sulfanilamides and penicillin was strongly in favor of the diagnosis of infectious mononucleosis, which was later proved by hematological or serological findings.

II. LARYNGEAL EDEMA IN INFECTIOUS MONONUCLEOSIS

CASE REPORT

A 30 year old white male was admitted to the hospital because of daily chills, fever, and generalized malaise of six days' duration. For the first time on the day

of admission he complained of slight sore throat, anorexia, and nausea, but had no vomiting. Upon admission the patient did not appear severely ill. The temperature was 99.4° F., the pulse rate 76 and the respiratory rate 20. The physical examination revealed a diffuse reddening of the throat with marked edema and bilateral cervical adenopathy, with nodes up to the size of a walnut. The liver was not palpable. The spleen was clearly palpable under the costal margin, its consistency firm, and its palpation did not cause pain.

The clinical impression of infectious mononucleosis was confirmed later by a leukocytic count of 12,000, with 19 per cent segmented neutrophils, 80 per cent lymphocytes and 1 per cent basophiles. Subsequent counts gave values of 8,500 to 6,000, with the lymphocytes decreasing from 75 per cent to a minimum of 27 per cent. The highest leukocytic count was the initial one of 12,000. Many of the lymphocytes were classified as "atypical," because of the structure of the nucleus and the vacuolization of the cytoplasm. Repeated heterophile antibody tests showed titers of 1:256, increasing to 1:1024 and later (one month after the onset of symptoms) decreasing to 1:256.

During the first day of hospitalization the sore throat increased rapidly. No improvement was obtained following the administration of 200,000 units of penicillin, in doses of 20,000 every three hours. The temperature maintained a remittent-intermittent character with a maximum of 102.6° F., then returned to normal on the seventh hospital day. The tenth hospital day the temperature rose again rapidly to 103.6° F. (pulse 112, respiratory rate 24). The patient was very uncomfortable and slightly dyspneic. All lymph nodes were markedly enlarged and the spleen was palpable 5 cm. below the costal margin. The throat appeared normal. This status continued for two days, with remissions of the temperature in the morning.

The twelfth hospital day the patient had great malaise and restlessness and was slightly dyspneic. He was given a small dose of a barbiturate (30 drops of Somnifen Roche), after which he fell asleep. Upon awakening a couple of hours later he complained of a choking sensation and of difficulty in swallowing. He assumed an orthopneic position, with frequent forced respirations, but had no stridor. On examination the throat was normal, but on laryngoscopy a marked edema was seen over both the arytenoids, more marked on the right side. There was no edema of the vocal cords. Moderate fever, generalized lymphadenopathy and splenic enlargement were still present. Ephedrine was administered by mouth ($\frac{3}{8}$ gr. every three hours) and by nasal instillation; calcium gluconate (10 c.c. of 10 per cent solution) was given intravenously repeatedly without influencing the edema.

The following day the laryngeal edema had progressed; there was marked injection of the epiglottis and of the arytenoids. In addition, on the right arytenoid there was a broad whitish membrane, resembling those covering the ulcerations frequently seen in the tonsils in cases of infectious mononucleosis. Posterior to the necrotic patch there was a small hemorrhagic area. •

The general condition of the patient showed no improvement for several days. On the fourteenth hospital day the hoarseness had increased, but the patient stated that the throat was less sore. There was marked increase in the ulceration of the arytenoids, by then involving both sides, but still more extensive on the right side. The epiglottis had become so swollen that on indirect laryngoscopy the false cords and the glottis could not be seen. At this time penicillin was again given, in a total dosage of 200,000 units (20,000 units every three hours), without any apparent improvement.

This situation continued unchanged for a few days. The seventeenth hospital day there was still considerable exudate on the arytenoids, but less edema of the epiglottis. The vocal cords were normal. The patient felt better and the temperature was normal.

The following day the temperature began to increase again. Respiratory distress and sore throat reappeared. The tonsils were very edematous and reddened. The swelling of the right arytenoid had decreased, but the membrane was still present and thick. The left arytenoid ballooned out and was of larger size than the right ever reached; however, no ulceration was visible on the left.

The nineteenth hospital day, great dysphagia appeared and the patient could swallow nothing. The throat was edematous with pear-shaped swelling of the uvula. Extensive ulcerations were present over both arytenoids and the interarytenoid area, extending into the glottis and down into the trachea. The maximum temperature that day was 103.2° F.

Two days later there was marked improvement and the temperature was normal. On laryngoscopy there were two small white spots over the left arytenoid, while the right was clear. Both were still edematous, but reduced to half the previous size. All the other structures of the larynx were normal.

From then on, the laryngeal inflammation subsided and the general condition of the patient improved. However, a low-grade fever persisted and the lymph nodes and spleen remained enlarged. Thirty-five days after admission the patient was transferred to another hospital for further treatment and convalescence.

COMMENT

In brief, this was the case of a young man suffering from typical severe infectious mononucleosis. The edema of the throat was very marked, yet not more severe than that seen in less serious cases. A short improvement was followed by a severe edematous and membranous laryngitis, causing great respiratory distress and dysphagia. The laryngitis appeared after the pharyngitis had subsided. The characters of the laryngeal inflammation resembled closely the changes seen previously in the pharynx of the same patient. After an improvement lasting a couple of days the pharyngitis and the laryngitis flared up again at the same time. The degree of obstruction was considerable, but at no time was there stridor, nor did the obstruction appear to cause too dangerous an interference with the respiration. For 15 days the advisability of an immediate tracheotomy was considered on several occasions and everything was prepared to perform it at a moment's notice. The subsequent course showed that in this case a tracheotomy was not necessary.

DISCUSSION

There is no doubt that many cases of infectious mononucleosis are erroneously diagnosed as streptococcal pharyngitis, common sore throat, Vincent's infection, grippe, or influenza. A large number of patients do not recover promptly after such common illnesses; it is possible that many are actually suffering from infectious mononucleosis, a benign disease, but of considerably longer duration.

The entire clinical picture of this disease has been discussed recently in different publications^{2, 3, 4, 5, 6} including a description of the various types of pharyngitis. However, in many cases the most common sore throat was described as due to a "diffuse injection of the throat," a vague term indeed. Occasional mention was made of pharyngeal edema in isolated cases of infectious mononucleosis,^{1, 7} but it seems that until now its importance for the clinical diagnosis has been overlooked.

The diagnosis of infectious mononucleosis is of importance, not only because of epidemiologic considerations, but also and principally because when this diagnosis is made the patient may be reassured, yet cautioned not to expect complete recovery within a few days.

In some patients the absence of sore throat tends to focus the attention upon other general diseases. In our experience the discovery of pharyngeal reddening and edema and/or the saccular shape of the uvula resulted in repeated laboratory tests and in a considerable increase in positive diagnoses.

The case of laryngeal edema reported here is of interest because this complication has not been described previously. A search of the literature revealed only one such diagnosis.⁸ In that case, however, no laryngoscopic examination was made and the site and type of lesion were not described.

The mechanism of the laryngeal edema was apparently inflammatory, since it did not subside when calcium and ephedrine were administered in the usual anti-allergic dosage. It could not have been a mechanical edema because of the presence of other inflammatory phenomena, including fever and great local reddening.

The etiology of the laryngitis cannot be stated. Unfortunately, no bacteriologic examination was performed. However, the lesions resembled closely those ordinarily seen in the throat of patients with infectious mononucleosis, and behaved so similarly, that it can be assumed that this laryngitis was due to the causative agent of infectious mononucleosis rather than to a secondary infection. This belief is confirmed by the lack of response to penicillin therapy and by the leukocytic count, which was always fairly low, with great predominance of lymphocytic cells.

It thus appears that infectious mononucleosis may severely affect the larynx and the trachea. This complication probably is not so rare as it would appear now. Once attention is called to its existence, it may be searched for and found more frequently, though most cases will not be so severe as the present one.

SUMMARY AND CONCLUSION

1. In infectious mononucleosis a marked inflammatory edema of the pharynx is frequently found, leading to swelling of the uvula which appears as a semi-transparent pear-shaped bag filled with clear fluid. This pharyngitis is sometimes present even when the patient does not complain of sore throat. It is believed that this constitutes a valuable sign for the presumptive clinical diagnosis of infectious mononucleosis.

2. A case of infectious mononucleosis is reported which was complicated by a severe edematous and membranous laryngitis, causing laryngeal obstruction.

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EDITORIAL

HISTOPLASMOSIS

IN the last decade there have been important additions to our knowledge concerning histoplasmosis which relate this infection to the daily work of the internist. In the first place, the rapidly increasing number of published cases of the clinically outspoken form of the disease suggests that this type of histoplasmosis should be considered as a definite possibility in certain syndromes. Secondly, a series of brilliant epidemiological studies indicates with a high degree of probability that clinically latent pulmonary infections with *Histoplasma capsulatum* account for various types of pulmonary infiltrates and calcifications previously considered specifically tuberculous in nature.

Between 1906, when the first case was described by Darling, and 1938, histoplasmosis was known only as a very rare and rapidly fatal disease. A lapse of 18 years occurred between Darling's report in 1908¹ of three cases in Panama and the next well-authenticated report, that of Watson and Riley (1926)² from Minnesota. In all, only 17 cases were reported up to 1939 and many of these cannot be considered proven.

During this period, however, 1906-1939, certain important advances had been made in our knowledge of the etiologic agent. Darling had believed that the organism to which he gave the name *Histoplasma capsulatum* was a protozoön akin to the Leishman-Donovan body. Da Rocha Lima in 1912 had examined Darling's preparation and suggested that *H. capsulatum* was a fungus. Renewed interest in the disease was awakened by De Monbreun's³ report in 1934 of the actual cultivation of the fungus from the blood and spleen of a proven case of histoplasmosis in a child in Tennessee.

The fungus, which in human tissues shows the yeast-like forms, develops on artificial media at room temperature filamentous forms which produce large, thick-walled, round, pyriform, tuberculate chlamydospores on aerial hyphae. Injection of these filamentous forms into dogs, puppies, rats, mice and monkeys has been shown to reproduce the disease. The yeast-like organisms are found in the reticulo-endothelial cells and the monocytes in granulomatous lesions which are most common in the liver, spleen, lungs, lymph nodes and adrenals. It was later shown that the mycelial and yeast phases of the life cycle of *Histoplasma capsulatum* could be completed by cultural methods without resorting to animal inoculation.⁴

¹ DARLING, S. T.: A fatal infectious disease resembling Kala-Azar found among natives of tropical America, Arch. Int. Med., 1908, ii, 107.

² RILEY, W. A., and WATSON, C. J.: Histoplasmosis of Darling: Case originating in Minnesota, Am. Jr. Trop. Med., 1926, vi, 271.

³ DE MONBREUN, W. A.: The cultivation and cultural characteristics of Darling's *Histoplasma capsulatum*, Am. Jr. Trop. Med., 1934, xiv, 93.

⁴ CONANT, N. F.: A cultural study of the life-cycle of *Histoplasma capsulatum* Darling 1906, Jr. Bact., 1941, xl, 563-574.

In the last decennium, clinical cases of histoplasmosis have been recognized far more frequently than heretofore. Parsons and Zarafonitis⁵ in 1945 published an analysis of 71 cases, and a review of the literature of the last three years suggests that not only are many further cases on record but that a large number of recognized cases exist which have not been reported. It has become apparent with the increase in number of reported cases that the disease is far more frequent in the eastern central states than in other parts of North America.

The generalized fatal form of histoplasmosis has been seen most frequently in infancy and childhood and after 40 years of age. It is more common in males. It is usually a febrile disease of subacute course with marked wasting leading to death within two years. In certain cases there are short periods of remission during which the patient is afebrile. Leukocytosis is not characteristic and in many cases a well marked leukopenia is observed. The findings on physical examination are very variable. The following are those which have been most commonly noted: hepatomegaly, splenomegaly, enlarged lymph nodes, lesions of the lungs, ulcerative lesions of the oropharynx, larynx, nares, intestinal tract, and ulcerative or papular lesions of the skin. It is obvious that the clinical picture at times may resemble lymphoblastoma, or aleukemic leukemia, or pulmonary or miliary tuberculosis. The deep ulcerative lesions of the tongue or oropharynx have suggested carcinoma. The not infrequent intestinal ulcerations have required differentiation from other causes of bloody diarrhea.^{6, 7}

The extreme variety in the clinical picture of histoplasmosis renders diagnosis from symptoms and signs a matter of conjecture. Recourse must be had to laboratory procedures. The important thing is to consider histoplasmosis as a diagnostic possibility.

In 1939 De Monbreun⁸ in discussing the paucity of case reports of histoplasmosis made the following statement: "It is probable . . . that the disease is more common than is generally supposed, possibly because the disease may occur in a relatively mild or non-fatal form and not be recognized. This presumption is in line with the report of Dickman which states that another fungus, *Coccidioides immitis*, which for some time has been known to cause the malignant and usually fatal disease coccidioidal granuloma, also gives rise to a much more common and milder form of the disease in California known as 'Valley fever' or 'Desert fever.'"

This prophetic statement of De Monbreun has been fully borne out in the last few years.

⁵ PARSONS, R. J., and ZARAFONITIS, C. J. D.: Histoplasmosis in man, Arch. Int. Med., 1945, lxxv, 1-23.

⁶ MILLER, E. H., KEDDIE, F. M., JOHNSTONE, H. G., and BOSTICK, W. L.: Histoplasmosis, cutaneous and mucomembranous lesions, etc., Arch. Dermat. and Syph., 1947, lvi; 715-739.

⁷ HENDERSON, R. G., PINKERTON, H., and MOORE, L. T.: *Histoplasma capsulatum* as a cause of chronic ulcerative enteritis, Jr. Am. Med. Assoc., 1942, cxviii, 885.

⁸ DE MONBREUN, W. A.: The dog as a natural host for *Histoplasma capsulatum*, case of histoplasmosis in this animal, Am. Jr. Trop. Med., 1939, xix, 565.

The chain of evidence suggesting a wide prevalence of a mild form of histoplasmosis is of great interest. It affords an excellent example of modern field investigations in epidemiology and of coöperative research.

Studies of the prevalence of pulmonary tuberculous infection had disclosed that an appreciable number of children with demonstrable calcified lesions in the lungs and hilar regions, interpreted as tuberculous, reacted negatively to tuberculin. Opie and his associates in 1926 and 1929, and Barnard, Amberson and Loew⁹ in 1931 had reported such data. However, in these earlier reports from the eastern section of the country the percentage of children with pulmonary calcification who were tuberculin negative was low (6 per cent).⁹ There was a tendency then to retain faith in the tuberculous nature of the pulmonary lesions and to interpret the negative tuberculin test as due to an unexplained loss of tuberculin allergy.

This interpretation was rudely shaken in the next 15 years by the reports of roentgenographic and tuberculin surveys in some of the southeastern states.^{10, 11, 12} The approach to the problem varied, some studying the frequency of pulmonary calcifications in tuberculin-positive and -negative groups and some the frequency of positive and negative tuberculin tests in groups found to show pulmonary calcification. These studies chiefly in childhood and adolescence were expanded by Long and Stearnes,¹³ whose study of Selective Service induction x-rays threw light on the prevalence of calcification* in the chests of young male adults from all over the United States. The results of these studies may be summarized as follows:

(a) It was shown that in a geographic area comprising the so-called Eastern Central States and a few states just west of the Mississippi the incidence of pulmonary calcification in children and young adults was exceptionally high. In inductees, for example, the range of incidence of calcifications in chest roentgen-rays varied from 6 per cent in Washington to 22 per cent in Missouri and 28 per cent in Kentucky. In 1945 Dillon, Gass and associates,¹⁴ in an extensive survey of high school students in Tennessee, found that in 25 counties the incidence of pulmonary calcification was 55 per cent or higher.

(b) In the geographic area above described it was abundantly proven that the incidence of tuberculin negativity in these cases of pulmonary calcification was too high to be explainable as due to anergy. In many sur-

⁹ BARNARD, M. W., AMBERSON, J. B., JR., and LOEW, M. K.: Tuberculosis in adolescents, *Am. Rev. Tuberc.*, 1931, xxiii, 593.

¹⁰ CRABTREE, J. A., HICKERSON, W. D., and HICKERSON, V. P.: Tuberculosis studies in Tennessee, *Am. Rev. Tuberc.*, 1933, xxviii, suppl. no. 6.

¹¹ GASS, R. S., GAULD, R. L., HARRISON, E. F., STEWART, H. C., and WILLIAMS, W. C.: Tuberculosis studies in Tennessee, *Am. Rev. Tuberc.*, 1938, xxxviii, 441.

¹² LUMSDEN, L. L., DEARING, W. P., and BROWN, R. A.: Questionable value of skin testing as a means of establishing an epidemiological index of tuberculous infection, *Am. Jr. Pub. Health*, 1939, xxix, 25.

¹³ LONG, E. R., and STEARNES, W. H.: Physical examination at induction, *Radiology*, 1943, xli, 144.

¹⁴ DILLON, A., GASS, R. S., HUBBARD, W. W., and HARRISON, E. F.: Results of the high-school tuberculosis program in Tennessee, *Jr. Tenn. Med. Assoc.*, 1945, xxxviii, 97.

veys far more of the children with pulmonary calcification were tuberculin-negative than were tuberculin-positive.¹⁵

Meanwhile on the Pacific coast knowledge had been gained concerning the early mild infections of the fungus disease Coccidioidomycosis. It had been shown that the pulmonary infiltrates characteristic of the primary infection were often followed by calcifications not distinguishable roentgenologically from tuberculosis: Skin sensitiveness to an antigen coccidioidin (a filtrate of a broth culture of the fungus) was found to persist for years after the clinical cure of the initial illness. Aronson, Saylor and Parr¹⁶ studied the Indians in Arizona and found that in northern Arizona the reservation Indians showed a low incidence of pulmonary calcification and a low incidence of positive reactions to coccidioidin; whereas in the southern reservation the incidence of both pulmonary calcification and positive coccidioidin tests was high. In view of this evidence that the fungus disease coccidioidomycosis was a cause of non-tuberculous pulmonary calcifications Christie and Peterson¹⁷ investigated the possibility that this disease might account for the high incidence of tuberculin-negative pulmonary calcification in the Tennessee area. They found, however, no evidence of coccidioidin sensitivity in 125 children tested and no evidence of clinical coccidioidomycosis.

It was becoming increasingly evident, as pointed out by Smith,¹⁸ that the endemic area of the fatal form of histoplasmosis coincided roughly with the geographic area of high incidence of pulmonary calcification in tuberculin-negative subjects. Christie and Peterson¹⁷ took the natural next step by preparing an antigen from a broth culture of *Histoplasma capsulatum* to which they gave the name histoplasmin. A study was then made of the chest roentgenograms and the skin sensitivity to histoplasmin and tuberculin of 181 children from Tennessee. This indicated plainly an association between histoplasmin sensitivity and tuberculin-negative pulmonary calcification. The same survey method inaugurated by Christie and Peterson received wider application by Palmer,^{19, 20} who added a histoplasmin sensitivity test to a roentgenologic and tuberculin survey of nurses on a nation wide basis. Palmer was able to show that in tuberculin-positive nurses the incidence of pulmonary calcification was 10.4 per cent, while in those nurses positive to histoplasmin calcification was found in 31.4 per cent. An even more important contribution was his analysis of data on 8,141 nurses which showed that the highest percentage of positive reactors to histoplasmin oc-

¹⁵ OLSEN, B. J., WRIGHT, W. H., and NOLAN, M. O.: Epidemiological study of calcified pulmonary lesions in an Ohio county, Pub. Health Rep., 1941, lvi, 2105.

¹⁶ ARONSON, J. D., SAYLOR, R. M., and PARR, E. I.: Relationship of coccidioidomycosis to calcified pulmonary nodules, Arch. Path., 1942, xxxiv, 31-48.

¹⁷ CHRISTIE, A., and PETERSON, J. C.: Pulmonary calcification in negative reactors to tuberculin, Am. Jr. Pub. Health, 1945, xxxv, 1131-1147.

¹⁸ SMITH, C. E.: Coccidioidomycosis, Med. Clin. N. Am., 1943, xxvii, 790-807.

¹⁹ PALMER, C. E.: Non-tuberculous pulmonary calcification and sensitivity to histoplasmin, Pub. Health Rep., 1945, lx, 513-520.

²⁰ PALMER, C. E.: Geographic differences in sensitivity to histoplasmin among student nurses, Pub. Health Rep., 1946, lxi, 475-487.

curred in the region including Tennessee, Kentucky, Arkansas, Missouri, Indiana and parts of Ohio, Illinois, Kansas and Louisiana.

Since these initial reports, extensive further studies^{21, 22, 23} have been carried out, in most part under the auspices of the United States Public Health Service. The geographic distribution of histoplasmin sensitivity and of pulmonary calcification has been intensively investigated. The attempt has been made to investigate the precalcification pulmonary lesions in children sensitive to histoplasmin but not to tuberculin. Seventy-two such cases showing pulmonary infiltrates were discovered in a survey of school children in Kansas City where the incidence of histoplasmin sensitivity is unusually high. The majority of these lesions are nodular foci in the lungs. Some show miliary dissemination. Slowly progressive calcification has been observed in certain instances. The authors, Furcolow and Montz²⁴ conclude that "in regions where histoplasmin sensitivity is widespread, pulmonary infiltrations as well as calcifications are frequently non-tuberculous and can be differentiated from tuberculosis at present only by skin tests."

A definite clinical symptomatology corresponding to the presence of these pulmonary infiltrates has not yet been described. Nor has it been possible to cultivate the organism in a series of such cases.

It is evident that under these circumstances the question of the specificity of the histoplasmin test is of prime importance. It has been pointed out by Emmons²⁵ and conceded by others that this skin test shows cross sensitivity with coccidioidin as well as with blastomycin and haplosporangin. The more recent work of Howell²⁶ indicates that cross reactions are intimately related to the strain of antigen and to the dosage used. If the critical titer of the antigen is determined and the proper concentration then employed the antigens are relatively specific.

At present most histoplasmin surveys are carried out with antigen provided by the National Institute of Health. The test consists of the intracutaneous injection of a dose of 0.1 c.c. of a dilution of 1 to 1,000. If the induration measures 5 or more millimeters 48 hours after injection the individual tested is considered a reactor.

Quite recently a complement fixation test has been described which appears to be quite specific.²⁷ The antigen employed was prepared from the yeast-like phase of the organism.

²¹ FEREBEE, S. H., and FURCOLOW, M. L.: Histoplasmin sensitivity among siblings, *Pub. Health Rep.*, 1947, *lxii*, 834-847.

²² FURCOLOW, M. L., HIGH, R. H., and ALLEN, M. F.: Some epidemiological aspects of sensitivity to histoplasmin and tuberculin, *Pub. Health Rep.*, 1946, *lxi*, 1132-1145.

²³ HIGH, R. H.: Disseminated pulmonary calcification, *Pub. Health Rep.*, 1947, *lxii*, 20-29.

²⁴ FURCOLOW, M. L., and MONTZ, H. L.: The roentgenographic appearance of persistent pulmonary infiltrates associated with sensitivity to histoplasmin, *Pub. Health Rep.*, 1947, *lxii*, 1711-1718.

²⁵ EMMONS, C. W., OLSON, B. J., and ELDRIDGE, W. W.: Studies of the role of fungi in pulmonary disease, *Pub. Health Rep.*, 1945, *lx*, 1383-1394.

²⁶ HOWELL, A.: Studies of fungus antigens. I., *Pub. Health Rep.*, 1947, *lxii*, 631-651.

²⁷ SALVIN, B. S.: Complement fixation studies in experimental histoplasmosis, *Proc. Soc. Exper. Biol. and Med.*, 1947, *lxvi*, 342-345.

The trend of evidence suggests strongly that in the endemic area described, subclinical infections with *Histoplasma capsulatum* have a high incidence rate and are frequently the cause of pulmonary infiltrations and calcified lesions. The direct proof that this is so awaits the conclusive demonstration that these patients harbor the specific organism.

In view of these developments concerning the multiple significances of infiltrates and calcifications in the lungs, we should more than ever press for bacteriological proof of the etiology of any apparently tuberculous pulmonary lesion.

REVIEWS

History of Medicine. By CECILIA C. METTLER. Edited by FRED A. METTLER. 1245 pages; 15 × 24 cm. The Blakiston Company, Philadelphia. 1947. Price, \$8.50.

According to the Editor's preface, the author of this correlative text devoted almost all her time and attention for over nine years to its production. The author's untimely death occurred a few days after she had completed the manuscript. She was Assistant Professor of Medical History, University of Georgia, School of Medicine. In his Foreword, Dr. Francis R. Packard says of the author, "Her death at a comparatively early age was a great loss to all students of the history of medicine."

The author in her preface makes the following statement concerning the practical value of a study of medical history, "As a means of providing a sense of perspective, of emphasizing the fundamental value of important medical principles, and of establishing a feeling of proportion among the component fields of medicine, the study of the development of medicine can scarcely be overestimated." With these points in mind the author states that the text was prepared, ". . . primarily for the physician teacher of medical history and for the medical student interested in an introduction to the field of medical history as a whole, and from a systematic standpoint." The author defends the position of the amateur medical historian and gives due emphasis to the importance of his rôle in the teaching of medical history.

The history of the following subjects is covered in detail with considerable quoted material from the author's full translations from original sources: Anatomy and Physiology, Pharmacology, Pathology and Bacteriology, Physical Diagnosis, Medicine, Neurology and Psychiatry, Venereology, Dermatology, Pediatrics, Surgery, Obstetrics and Gynecology, Ophthalmology, and Otology and Rhinolaryngology. Chapters on these subjects trace their beginnings in the past to about the middle of the nineteenth century. The author states that she was forced to limit the work to outstanding facts presented as briefly as possible. Thus, the physician will find a comprehensive review of the history of the fundamental fields of medicine in well organized chapters, and the medical student may easily follow the history of the subject he is studying. Dr. Packard further says of the work, "It presents many original features, most especially important of which are the full translations from original sources illustrating the most important works of the Greek, Latin, and Arabic authors."

The work is attractively bound, and is printed in two column text. There are but 16 illustrations, the Editor having purposely avoided including more in order to keep the size of the book within reasonable bounds. Boldface type is employed in the text when mention of an individual is first made. A list of general references precedes the Table of Contents. There are 15 chapters, at the end of each of which is an excellent bibliography, and there are copious references given as page footnotes. An alphabetical listing of all persons mentioned and a splendid general subject index conclude the volume. The author's style is scholarly but very readable, and her approach is refreshing.

This monumental work is warmly recommended to all physicians and medical students.

J. E. S.

Tuberculosis as It Comes and Goes. By EDWARD W. HAYES, M.D., F.A.C.P. 220 pages; 15 × 23 cm. Charles C. Thomas, Springfield, Illinois. 1947. Price, \$3.75.

The author has written this book for his patients and for the patients' friends; that they may better understand tuberculosis, and through such understanding be bet-

ter able to conquer the disease. In writing the book, Dr. Hayes has drawn on his personal experience as a patient on the "cure."

The author guides the reader through a description of the tubercle bacillus and its works, through the theories of infection and the ideas of control of infection. The distinction between the infection and the disease is clearly presented. The observation is made that infection is gradually decreasing with the decrease of the disease.

A simple classification of the disease is presented. Schematic representations are furnished of the types of disease. The elements of diagnosis are briefly described.

The chapter on treatment is splendidly written. The patient who has read this chapter will understand what is required when he is told that rest is necessary in the treatment of the disease. The section on sanatorium versus home treatment presents in excellent fashion the first problem that the newly diagnosed tuberculous patient must face. Climate and heliotherapy are discussed and placed in their proper perspective.

The various methods of mechanical therapy are described simply and with just enough detail so that the patient will have some understanding of what the physician is endeavoring to accomplish. Again in this section schematic representations are used to illustrate the effects of compression therapy of the varied types.

There are chapters on the complications of tuberculosis, on pulmonary hemorrhage and on pregnancy and tuberculosis. Throughout the attempt is made to present the facts honestly but so as to remove the fear connected with uncertainty and doubt from the mind of the patient.

The last chapters are written by Dr. De Ryche, a patient of Dr. Hayes. These chapters describe this patient's struggle with the first diagnosis of tuberculosis, his acceptance of his ordeal and finally the manner in which he was able to cope successfully with his problem. The patient who reads these chapters will find in its words his own fears, his hopes and finally may find the means whereby he too can make the period of cure a period of mental and physical gain.

Dr. Hayes' book may be recommended without reservation to the tuberculous. It will amplify their knowledge and enable them to understand what the doctor has told them. And further it may furnish them with a plan that may make easier the trial that tuberculosis must be. The physician who treats the tuberculous may profitably read this book so that he may better understand the fears that beset his patients and may be better able to allay these fears.

M. W. J.

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Brief Psychotherapy: A Handbook for Physicians on the Clinical Aspects of Neuroses.

By BERTRAND S. FROHMAN, M. D., with the collaboration of EVELYN P. FROHMAN. Foreword by WALTER C. ALVAREZ, M.D. 265 pages; 20.5 × 14 cm. 1948. Lea & Febiger, Philadelphia. Price, \$4.00.

Bright's Disease. Chapter X (Supplement to the Oxford Loose Leaf Medicine).

By HENRY A. CHRISTIAN. 385 pages; 25.5 × 19 cm. (paper bound). 1947. Oxford University Press, New York. Price: Furnished only to subscribers to the complete set of Oxford Loose-Leaf Medicine.

- Communicable Diseases* (2nd Ed.). By FRANKLIN H. TOP, A.B., M.D., M.P.H., F.A.C.P., Medical Director, Herman Kiefer Hospital, etc., and COLLABORATORS. 992 pages; 22.5 × 14.5 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, \$9.50.
- The Epithelia of Woman's Reproductive Organs: A Correlative Study of Cyclic Changes.* By GEORGE N. PAPANICOLAOU, M.D., Ph.D., Professor of Clinical Anatomy, Cornell University Medical College; HERBERT F. TRAUT, M.D., Professor of Obstetrics and Gynecology, University of California Medical School, and ANDREW A. MARCHETTI, M.D., Associate Professor of Obstetrics and Gynecology, Cornell University Medical College. 53 pages (plus 22 colored plates); 28.5 × 20.5 cm. 1948. The Commonwealth Fund, New York. Price, \$10.00.
- Modern Treatment of Peptic Ulcer.* By ASHER WINKELSTEIN, M.D., B.S., Associate Physician for Gastro-enterology and Physician in Charge of the Gastrointestinal Clinic, The Mount Sinai Hospital, New York City, etc. 205 pages; 22 × 14.5 cm. 1948. Oxford University Press, New York. Price, \$4.00.
- Occupational Medicine and Industrial Hygiene.* By RUTHERFORD T. JOHNSTONE, A.B., M.D., Consultant in Industrial Health; Lecturer at the University of California, Los Angeles, etc. 604 pages; 25 × 17 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, \$10.00.
- The Rh Factor in the Clinic and the Laboratory.* JOSEPH M. HILL, M.D., and WILLIAM DAMESHEK, M.D., Editors. 192 pages; 26 × 18 cm. 1948. Grune & Stratton, Inc., New York. Price, \$4.25. (Special issue No. 2 of Blood, The Journal of Hematology.)
- Shoot That Needle Straight!* By ROBERT RANTOUL. 220 pages; 20 × 14 cm. 1947. Bruce Humphries, Inc., Boston. Price, \$2.75.
- Symposium on Medicolegal Problems, Under the Co-sponsorship of the Institute of Medicine of Chicago and the Chicago Bar Association.* Edited by SAMUEL A. LEVINSON, M.D., Ph.D., University of Illinois College of Medicine, for The Committees of the Institute of Medicine and The Chicago Bar Association. 255 pages; 20 × 13 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, \$5.00.
- Textbook of Endocrinology.* By HANS SELYE, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada), Professor and Director of the Institut de Medecine et de Chirurgie experimentales, Universite de Montreal; with a preface by Professor BERNARDO A. HOUSSAY, Prix Nobel, 1947, Buenos Aires, Argentina. 914 pages; 26 × 18 cm. 1947. Acta Endocrinologica, Universite de Montreal, Montreal. Price, \$10.24.
- Topics in Physical Chemistry: A Supplementary Text for Students of Medicine.* By W. MANSFIELD CLARK, Ph.D., Sc.D., DeLamar Professor of Physiological Chemistry, The School of Medicine, The Johns Hopkins University. 738 pages; 23.5 × 16.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$10.00.
- Tuberculosis: A Discussion of Phthysiogenesis, Immunology, Pathologic Physiology, Diagnosis, and Treatment.* By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P., Emeritus Professor of Medicine, University of Southern California, the School of Medicine, etc. 597 pages; 25.5 × 17.5 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, \$12.00.

COLLEGE NEWS NOTES

A.C.P. POSTGRADUATE COURSES

Spring 1948 Program

Course No. 1, Medical Aspects of Radioactivity, at the U. S. Naval Medical School, was concluded on February 28, 1948, with a registration of 22 physicians from the College and a much larger number from the Medical Corps of the U. S. Army and the U. S. Navy. The course has been reported to have been exceedingly successful, especially in view of the fact that it differed from previous courses by covering certain clinical phases of the subject. It is anticipated that the demand for this course will grow and that the College will repeat it again in the future.

By the time this announcement appears in press, Course No. 2, Physical Medicine for the Internist, at the Mayo Foundation and Mayo Clinic, March 22-26, under Dr. Frank Krusen, F.A.C.P., Director, will have been concluded. At the present, there are 19 registrants but it is anticipated several additional physicians will register before the course opens.

In the case of Course No. 3, Cardiovascular Diseases, at the University of Southern California School of Medicine, Los Angeles, April 12-17, under Dr. George C. Griffith, F.A.C.P., Director, the registration at this time is 47 with prospects of several additions before the course opens.

Course No. 4, Electrocardiography: Basic Principles and Interpretation, at the Massachusetts General Hospital, May 10-15, under Dr. Conger Williams, Director, has been closed for some time with a maximal registration of 26. The demand for this course has been so great that the College will either repeat it or schedule another course in electrocardiography in the autumn or next spring.

Course No. 5, Internal Medicine, at the Gallinger Municipal Hospital, May 17-22, under Dr. Wallace M. Yater, F.A.C.P., Director, is still open for registration since facilities are sufficiently great to accommodate up to 100. Present registration, 37.

Course No. 6, Clinical Allergy, at the Roosevelt Hospital, New York, May 17-28, under Dr. Robert A. Cooke, F.A.C.P., Director, was limited to eight physicians and has been filled for several weeks.

Course No. 7, Clinical Neurology, at the Jefferson Medical College of Philadelphia, May 24-28, under Dr. Bernard J. Alpers, F.A.C.P., Director, has a current registration of 24 but facilities for as many as 75. The course is offered for those without special training in neurology and is directed toward a discussion of pertinent problems in clinical neurology, illustrated by case material wherever possible. Emphasis will be placed on the diagnosis and treatment of nervous disorders. This is one of the very fine courses arranged for the College and members are encouraged to register early.

Course No. 8, Physiological Basis for Internal Medicine, at the University of Illinois College of Medicine, May 31-June 5, under Dr. A. C. Ivy, F.A.C.P., Director, already has a registration of 91 but facilities are adequate to accommodate an even larger number. Therefore, registration is still open.

Course No. 9, Diabetes and General Medicine, at the New England Deaconess Hospital, Boston, July 12-16, under Dr. Elliott P. Joslin, F.A.C.P., Director, has a present registration of 30 but facilities are adequate to accommodate up to 75. The subject matter of this course is planned to give the fundamental physiologic and pathologic background of diabetes, coordinated with the clinical features and the relationship of diabetes and general medicine. During the week, two excursions are planned to diabetic camps for more practical demonstrations. Members are urged to register early.

Courses under Consideration for Autumn, 1948

The Advisory Committee on Postgraduate Courses will meet during the San Francisco Annual Session of the College in April definitely to make up the autumn schedule. Those courses particularly under consideration are as follows:

Blood Disorders—Ohio State University College of Medicine, Columbus, under Dr. Charles A. Doan, F.A.C.P., and Dr. B. K. Wiseman, F.A.C.P.—one week.

Cardiology—

(1) A two-week course in cardiology during August may be held at the National Institute of Cardiology in Mexico City under the direction of Dr. Ignacio Chavez, F.A.C.P., with the instructional staff being made up of a number of outstanding Mexican teachers who speak English, supplemented by several distinguished guest teachers from the U. S. Sessions will be held in the mornings daily, with the afternoons free for entertainment, sightseeing and visits to other institutions. This course presents an opportunity for a most enjoyable two weeks' vacation, partly devoted to study and observation of methods in our neighboring Republic. Wives and members of the physicians' families are invited, and adequate hotel accommodations will be available. Those interested in this course are requested to communicate at once with the Executive Secretary of the College so that some definite estimate can be prepared for the Director and the hotels.

(2) Recent Advances in the Diagnosis and Treatment of Cardiovascular Diseases, Massachusetts General Hospital, Boston, Dr. Paul D. White, F.A.C.P., Director—one week.

(3) Electrocardiography—Emory University School of Medicine, Atlanta, Ga., Dr. R. Bruce Logue, F.A.C.P., Director—one week.

Endocrinology—Chicago Institutions, Dr. Willard O. Thompson, F.A.C.P., Director—one week.

Gastro-enterology—

(1) University of Chicago, Dr. Walter L. Palmer, F.A.C.P., Director—one week.

(2) University of Pennsylvania Graduate School of Medicine, Philadelphia, Dr. Henry L. Bockus, F.A.C.P., Director—one week.

(3) University of California Medical School and Stanford University School of Medicine, Dr. Theodore L. Althausen, F.A.C.P., and Dr. Dwight L. Wilbur, F.A.C.P., Directors—one week.

It is not anticipated that all three of the above courses in gastroenterology will be actually arranged for the autumn of 1948, but probably two will be selected, one of which will be the course at San Francisco.

Internal Medicine—

(1) University of Michigan Medical School, Ann Arbor, Dr. Cyrus C. Sturgis, F.A.C.P., Director—one or two weeks.

(2) University of Cincinnati College of Medicine, Dr. M. A. Blankenhorn, F.A.C.P., Director. This course will be entitled "Internal Medicine with Emphasis on Pathological Physiology," will be limited to 40 registrants and will probably be scheduled for October 11-15.

(3) University of Pittsburgh School of Medicine, Pittsburgh, Pa., Dr. R. R. Snowden, Director—2 weeks, Sept. 20-Oct. 2; limited to 25.

Other possibilities under consideration are courses in internal medicine under Dr. Cecil Watson, F.A.C.P., University of Minnesota, and one under Dr. Maurice C. Pincoffs, F.A.C.P., University of Maryland School of Medicine, Baltimore.

Physiological Basis for Internal Medicine—University of Pennsylvania Graduate School of Medicine, Dr. Julius H. Comroe, Jr., F.A.C.P., Director—one week.

Psychosomatic Medicine—University of Colorado Medical Center and the Colorado Psychopathic Hospital, Denver, Dr. Franklin G. Ebaugh, F.A.C.P., Director—one week. (Members interested particularly in this course are requested to communicate now with the Executive Secretary of the College because it is desired to determine in advance the number who would wish to take this course.)

Other Courses—Members are invited to send in suggestions for courses especially desired with respect not only to subject, but also to location, director, duration and dates. Address suggestions to E. R. Loveland, Executive Secretary, The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

ADDITIONAL LIFE MEMBERS

The American College of Physicians takes pleasure in announcing that the following Fellows became Life Members of the College by recent subscription:

Roland Davison, San Francisco, Calif.
 Paul A. Draper, Colorado Springs, Colo.
 Samuel Epstein, Brooklyn, N. Y.
 George M. Laning, Detroit, Mich.
 Marie Ortmayer, Chicago, Ill.
 Joseph T. Roberts, Little Rock, Ark.
 John W. Skinner, Yakima, Wash.
 Reuben A. Solomon, Indianapolis, Ind.
 William D. Stubenbord, New York, N. Y.
 Lester Taylor, Cleveland, Ohio.
 Howard F. West, Los Angeles, Calif.

SPECIALTY BOARD EXAMINATIONS

American Board of Internal Medicine, 1 W. Main St., Madison 3, Wis.; William A. Werrell, M.D., Assistant Secretary-Treasurer. Oral examinations will be conducted in Chicago in June, 1948, immediately before the Convention of the American Medical Association (closing date, February 1). The next written examination will be on October 18, 1948, with closing date for registration on June 1.

The American Board of Pediatrics, Inc., 718 Royal Union Bldg., Des Moines, Iowa; Lee F. Hill, M.D., Secretary-Treasurer. The next oral examination will take place in Chicago on June 25-27, 1948.

The American Board of Physical Medicine, 30 N. Michigan Ave., Chicago 2, Ill.; Robert L. Bennett, M.D., Secretary-Treasurer. The next examination period will be two days prior to the Meeting of the American Medical Association, June, 1948, Chicago, Ill.

INTERIM BOARD FOR PREVENTIVE MEDICINE

The Surgeons General of the Army, Navy and Public Health Service have announced the formation of an "Interim Board" of Preventive Medicine, composed of the following distinguished specialists in that field: Drs. Ernest L. Stebbins, Johns Hopkins University School of Hygiene and Public Health; Wilton L. Halverson, California Department of Public Health; Thomas Francis, Jr., University of Michigan

School of Public Health; Harry S. Mustard, Commissioner of Health, New York City; Gaylord W. Anderson, University of Minnesota School of Public Health; Hugo Muench, Harvard School of Public Health; James Crabtree, Deputy Surgeon General, U. S. Public Health Service; Colonel Tom F. Whayne, Chief, Preventive Medicine Division, Office of the Surgeon General, U. S. Army; and Captain Otto L. Burton, F.A.C.P., Chief, Preventive Medicine Division, Bureau of Medicine and Surgery, U. S. Navy. Dr. Stebbins has been elected chairman of the Board. The Board is engaged in drafting a preliminary statement of requirements for certification.

PROPOSALS FOR MEMBERSHIP, A.C.P.

The regulations and by-laws of the American College of Physicians specify that proposals of candidates must be filed in the Executive Offices at least sixty days in advance of action by the Committee on Credentials. Therefore, proposals for membership submitted after February 18, 1948, could not be presented for action at the San Francisco Annual Session in April, but will be presented for action at the next succeeding meeting of the Committee in the autumn. However, all such candidates were cordially invited to attend the San Francisco Annual Session and provided with a program and courtesy card of admission.

The 76th Annual Meeting of the American Public Health Association will take place at Boston, Mass., November 8-12, 1948.

The First International Poliomyelitis Conference will take place at the Waldorf-Astoria Hotel, New York, N. Y., July 12-17, 1948, under the sponsorship of The National Foundation for Infantile Paralysis. Details of the program may be secured from Mr. Stanley E. Henwood, Executive Secretary, Room 571, Waldorf-Astoria Hotel, New York 22, N. Y.

J. C. Geiger, M.D., F.A.C.P., San Francisco, Calif., has recently been honored by the Surgeon General, U. S. Navy, by a certificate of appreciation of exceptional services performed during the recent war.

Leon Unger, M.D., F.A.C.P., Chicago, Ill., recently delivered lectures in Mexico before the Sociedad Mexicana de Alergistas, in San Luis Potosi, and before the staff of the Childrens' Hospital of Mexico City.

Virgil P. Sydenstricker, M.D., F.A.C.P., Augusta, Ga., has been elected to succeed the late John H. Musser, M.D., M.A.C.P., as a member of the Council on Medical Education and Hospitals of the American Medical Association.

The resignation of James J. Waring, M.D., F.A.C.P., as administrative head of the Department of Medicine of the University of Colorado School of Medicine, was recently reported. The report stated that Dr. Waring will continue to serve as Professor of Medicine.

OBITUARIES

DR. JULES C. ABELS

Dr. Jules C. Abels, of New York City, died suddenly on June 13, 1947. Dr. Abels had been elected an Associate of the American College of Physicians in October of 1946. His work at the Memorial Hospital in New York City had won him the reputation of a brilliant young investigator and clinician.

Dr. Abels was a graduate of Columbia University and of the New York University College of Medicine. As an undergraduate, he made original contributions in biochemistry and, in 1935-1936, he was a New York University Research Fellow in biochemistry. While still a medical student, he also assisted at the Rockefeller Institute for Medical Research as a volunteer chemist. Dr. Abels interned in the Sinai Hospital, Baltimore, 1939-1940 and then went to the Memorial Hospital as a Finney-Howell Fellow. He became Clinical Assistant and Assistant Attending Physician in the hospital and conducted research in the abnormality of nutrition which characterizes some forms of cancer. He was also Consultant in Endocrinology to the Meadowbrook Hospital, Hempstead, N. Y. and a member of the courtesy staffs of Doctors and Park East Hospitals, New York City, and of Horace Harding Hospital, Elmhurst, N. Y.

Dr. Abels was a member of the American Association of Cancer Research, Society for Experimental Medicine and Biology, American Society for Experimental Pathology, Society for the Study of Blood, American Association for the Advancement of Science, the New York State and County Medical Societies, and the American Medical Association.

DR. CHARLES B. COGGIN

Charles Benjamin Coggin, M.D., F.A.C.P., well known Los Angeles physician, died at the age of forty on Saturday, January 10, 1948, at the University of California Hospital in San Francisco, following an emergency operation.

Dr. Coggin lived at 602 Cahuenga Blvd., Los Angeles, and was associated with Eugene L. Armstrong, M.D., F.A.C.P., at 1930 Wilshire Blvd. He took his academic work at Washington Missionary College in 1929, where he received his A.B. degree, and was graduated from the College of Medical Evangelists at Loma Linda in 1935.

From 1935 to 1938 Dr. Coggin was a resident physician in internal medicine and pathology at the Los Angeles County General Hospital. He served in the Army as a major from 1941 to 1945, and at the time of his discharge held the rank of lieutenant colonel. Dr. Coggin saw service in the Aleutians.

Dr. Coggin was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. He was also a Fellow of the American Medical Association, and a member of the Hollywood Academy of Medicine and the Los Angeles Athletic Club. Dr. Coggin was a senior visiting physician at the Los Angeles County General Hospital and an associate professor in the College of Medical Evangelists.

LELAND HAWKINS, M.D., F.A.C.P.,

Governor for Southern California

DR. FREDERIC CHARLES CONWAY

Dr. Frederic C. Conway, a native of Albany, N. Y., died suddenly in his sleep on December 7, 1947, at the age of sixty-five, apparently from coronary occlusion.

Dr. Conway attended the public schools of Albany and then entered the Albany Medical College, from which he received the M.D. degree in 1906. His practice was limited to Internal Medicine and Cardiology. He served the Albany Medical College from 1907 until his death, first as Clinical Assistant, and then, successively, as Instructor in Physical Diagnosis, Instructor in Medicine, and Associate Professor of Medicine.

Dr. Conway's hospital appointments included the following: Attending Physician, Anthony N. Brady Maternity Home and St. Peter's Hospital; Physician-in-Charge, Ann Lee Home and Preventorium. He also served St. Peter's Hospital as Chief of Staff from 1934 to 1945. Dr. Conway was a member of the New York State Examining Board for Retirement of State Officials.

Dr. Conway had been a Fellow of the American College of Physicians since 1916. He was one of its earliest members.

DR. ALEXANDER R. HALL

Dr. Alexander R. Hall of St. Paul, Minn., died November 27, 1947, at the age of seventy-three. Dr. Hall became an Associate of the American College of Physicians and a Member of the American Congress on Internal Medicine in 1920.

A graduate of the McGill University Faculty of Medicine in 1900, Dr. Hall later became affiliated as Assistant Professor of Medicine with the University of Minnesota Medical School and with the Miller Clinic in St. Paul. He was a member of the staff of Ancker Hospital. His society memberships included the American Medical and Minnesota State Medical Associations, and the Ramsey County Medical Society. He was a former President of the Minnesota Academy of Medicine.

DR. WILLIAM H. MARSHALL

William Henderson Marshall, M.D., F.A.C.P., of Flint, Mich., died of coronary occlusion on January 8, 1948.

Born in Brampton, Ontario, March 24, 1874, Dr. Marshall received his M.D. degree from the University of Toronto in 1901. During the next several months he served as Resident Pathologist in the Toronto General Hospital. He came to the United States in 1902 and started the practice of medicine in southeastern Kansas. One year later, he moved to Boyne City, Mich., where he continued practice until he enlisted in the British Army in 1915. The years of 1906 and 1910 were spent in Edinburgh and London in intensive postgraduate work. In 1915 he enlisted in the Royal Army Medical Corps of the British Army with the rank of captain. In 1918, Dr. Marshall left the British Army and enlisted in the medical corps of the United States Army, where he attained his majority. Late that year, he came to Flint where he continued medical practice until his death.

Dr. Marshall's enthusiasm and keen interest in the advancement of medical science were recognized by many honors bestowed upon him. He was President of the Northern Tri-State Medical Association in 1936, a past President and Secretary of the Genesee County Medical Society, Chief of the Medical Department of Hurley Hospital for 15 years and, at the time of his death, Director-emeritus of that Department. He was a past President of the Michigan Trudeau Society, a member of the Genesee County Medical Society, Flint Academy of Medicine, and the Michigan

State Medical Society. He was a Fellow of the American Medical Association and, since 1921, of the American College of Physicians. In 1934 he headed a survey on the cost of medical care for the Michigan State Medical Society which involved questionnaires sent to 5,585 physicians. For six years, he served on the Michigan State Board of Registration in Medicine. He contributed various articles to the Medical literature and was a regular attendant at local, state and national medical meetings.

A skilled physician and a kindly gentleman, who maintained the highest ideals of our profession, Dr. Marshall will be greatly missed by his colleagues and the medical profession in general.

M. S. CHAMBERS, M.D., F.A.C.P.

DR. JUDSON P. PENDLETON

Judson Philbrook Pendleton, M.D., F.A.C.P., a pediatrician who practiced in Brooklyn for nearly fifty years, died there recently at the age of seventy-four.

Dr. Pendleton was born at Isleboro, Maine, a descendant of Bryan Pendleton who came to the American colonies in 1632. He received his medical degree from the College of Physicians and Surgeons of Columbia University in 1898. Dr. Pendleton was consultant in Contagious Diseases to the Kingston Avenue Hospital, and Consultant in Pediatrics to the Coney Island Hospital, of which he was, for many years, President of the Board.

Dr. Pendleton's society memberships included the Medical Society of the County of Kings, Medical Association of Greater City of New York, The Medical Society of the State of New York, American Medical Association. He served as President of the Brooklyn Pediatric Society in 1929, the year of his election to Fellowship in the American College of Physicians.

Dr. Pendleton was a distinguished physician who has left a lasting mark among his confreres.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. WILLIAM DAVID SANSUM

William David Sansum, M.D., F.A.C.P., died in his research laboratory in the Santa Barbara Cottage Hospital, Santa Barbara, Calif., of a pontine hemorrhage on January 5, 1948.

Dr. Sansum was born at Baraboo, Wis., on September 25, 1880. Born in humble circumstances, he taught in the public schools of Wisconsin for more than four years, thus enabling himself to obtain the degree of B.S. from the University of Wisconsin in 1912 and an M.S. degree in 1913. He received his M.D. degree cum laude from Rush Medical College in 1915. While a student at Rush Medical College, he was also a Fellow of the Sprague Memorial Institute and continued this connection until 1920. He was also an instructor on the Rush Medical faculty from 1918 to 1920. He was an intern in the Presbyterian Hospital of Chicago for two years, beginning March 1917. During his association with the Sprague Institute he worked almost entirely on problems related to carbohydrate metabolism and diabetes. After his graduation he was associated with Dr. Roland T. Woodyatt and his interest in diabetes was further stimulated. In 1920, he was brought to Santa Barbara by the Directors of the Santa Barbara Cottage Hospital to become Director of the Potter Metabolic Clinic and Director of Metabolic Research in the Santa Barbara Cottage Hospital. In this capacity, he was intimately associated with the early work in the isolation of insulin and, through his interest and energy, he and his associates produced the first insulin avail-

able to patients in the western United States. Continuing his original work in diabetes, he and his associates published in the Journal of the American Medical Association in 1926 the first article in the American literature on the use of high carbohydrate diets in the treatment of diabetes mellitus.

Throughout his life he remained an ardent research worker and teacher. He was actively interested in the teaching of the resident staff of the hospitals with which he was associated. In 1927, he began to surround himself with younger physicians to aid in the handling of his growing practice. In 1931, he founded the Sansum Clinic which still bears his name. As a part of his teaching program, he also conducted lectures for patients, attempting to give them an insight into the causes of some of the more common ailments. He felt that this teaching was an integral part of the practice of medicine. He was author of more than seventy medical papers and books, from 1912 to 1948.

He will always be remembered by his colleagues and patients for his wonderful kindness, sympathy and fairness in all his relations, and for his truly remarkable insight into the problems and anxieties of others.

A past president of the Santa Barbara County Medical Society, past chairman of the staff of the Santa Barbara Cottage Hospital, and former Councillor of the American Diabetes Association, Dr. Sansum was also a member of the California and American Medical Associations, California Society for the Promotion of Medical Research, Society for Experimental Biology and Medicine, The American Medical Editors and Authors Association, and Association for the Study of Internal Secretions. He was a Fellow and Life Member of the American College of Physicians.

LELAND HAWKINS, M.D., F.A.C.P.,

Governor for Southern California

DR. PHILIPP SCHONWALD

Philipp Schonwald, M.D., F.A.C.P., came to this country from Austria in 1921. He had received his medical degree from the University of Vienna in 1905, and had been Medical Director of the Sanatorium Grimmerstein, in Lower Austria, from 1910 to 1921.

Acting on the advice of an uncle who had visited the United States, Dr. Schonwald established his practice in the Pacific Northwest, in Seattle. He became a member of the staffs of the Riverton Hospital for Chest Diseases and the King County Tuberculosis Hospital, serving the latter institution as Chief of Staff. He was also a member of the teaching staff of the Swedish Hospital Nursing School.

Dr. Schonwald was greatly interested in the investigation of problems of tuberculous and non-tuberculous chest diseases. It is said that he was one of the first physicians in Vienna to employ x-ray equipment, and that he was a pioneer in the use of thoracoplasty, pneumothorax and intrapleural pneumolysis. He conducted studies of allergenic bacteria, molds and fungi, and on the production of antibiotic substances by molds and fungi.

Dr. Schonwald was a cultured person: an accomplished linguist and musician, interested also in horticulture and painting.

Dr. Schonwald became a Fellow of the American College of Physicians in 1928. He was also a Fellow of the American Medical Association, and a member of the King County and Washington State Medical Societies as well as of the American Academy of Tuberculosis Physicians and the American College of Chest Physicians.

Dr. Schonwald's death on December 20, 1947, followed by six years a stroke which had caused a left hemiplegia.

DR. NOEL CATCHING WOMACK

Noel Catching Womack of Pocahtonias, Miss., died December 26, 1947. Ill health had caused his retirement from active practice the previous June. Dr. Womack became a Fellow of the American College of Physicians in 1924.

Born at Dibrell, Tenn., August 26, 1879, Dr. Womack attended Dibrell Normal College and the University of Tennessee and completed his medical course at the Jefferson Medical College of Philadelphia in 1904. Following internship at the Reading General Hospital, Reading, Pa., he entered general practice in Jackson, Miss., in 1906. In 1913-14 he undertook further studies in Pediatrics at the New York Post-Graduate Medical School and Hospital. He later became a Diplomate of the American Board of Internal Medicine.

Dr. Womack was founder and President of the Jackson Infirmary and headed its Department of Pediatrics as well as that of the Mississippi State Charity Hospital. He was also Consultant in Pediatrics to the Mississippi Baptist Hospital and to the Mississippi Tubercular Sanatorium (Magee). He was an organizer and the first President of the Mississippi Pediatric Society, and a charter member of the American Academy of Pediatrics. Dr. Womack was also a member of the International Congress of Pediatrics, the Central Medical Society, and of the Mississippi State, Southern and American Medical Associations.

Dr. Womack was jovial, friendly and likeable, and most active in his chosen field. He stood for the highest and the best. He will be missed by his many associates, friends and patients, by whom he was highly esteemed.

JOHN G. ARCHER, M.D., F.A.C.P.,
Governor for Mississippi

DR. PAUL JAMES CONNOR

With the death of Dr. Paul James Connor of Denver, Colorado has lost one of its most active and capable internists. Dr. Connor was born in Madisonville, Texas, in 1887. He attended the Agricultural and Mechanical College of Texas before entering the University of Texas School of Medicine, from which he graduated in 1912. He came to Colorado from the Ancon Hospital, Canal Zone, in 1920. He was active on the staffs of the Presbyterian, St. Luke's and Mercy Hospitals, of Denver.

A diplomate of the American Board of Internal Medicine, Dr. Connor was particularly interested in endocrinology. He was also very active in the public health work of Colorado, and was President of the State Board of Health in 1931.

He was a member of the Denver City and County and Colorado State Medical Societies, the Inter-State Post Graduate Medical Association of North America, the American Association for the Study of Goiter, the American Diabetes Association, the Association for the Study of Internal Secretions and was a Fellow of the American Medical Association. Dr. Connor had been a Fellow of the American College of Physicians since 1931.

WARD DARLEY, JR., M.D., F.A.C.P.,
Governor for Colorado

DR. HENRY CLAY LONG

Dr. Henry Clay Long, one of Tennessee's well-known medical consultants, died at his home in Knoxville, September 14, 1947.

Dr. Long was born in Marion County, Tenn., October 15, 1878. He attended Pryor Institute and then received his M.D. from Vanderbilt in 1914. His ability as a student is amply shown by his election as a member of the honorary medical society, Alpha Omega Alpha.

His postgraduate study was at the Riverside and Bellevue Hospitals, New York, N. Y., and the New York Post-Graduate Medical School and Hospital. He was a diplomate of the American Board of Internal Medicine:

Dr. Long served in the Army in World War I.

He was a past president of the Knoxville Academy of Medicine, and a Member of the East Tennessee Medical Society, The Tennessee State Medical Society, and the Southern Medical Association. Dr. Long had been a Fellow of the American College of Physicians since 1936.

Dr. Long was a hard worker, a thorough student, and a conscientious physician.

WILLIAM C. CHANEY, M.D., F.A.C.P.,
Governor for Tennessee

DR. SAMUEL EDGAR MUNSON

Samuel E. Munson, M.D., F.A.C.P., dean of the medical profession of Springfield, Ill., died on October 2, 1947, at the Memorial Hospital there at the age of 81, following a long illness. He is survived by his wife and by his daughter, Miss Mary Munson.

Born in 1866 on a farm in Meechanicsburg Township, Sangamon County, Ill., Samuel E. Munson was the son of Joel M. and Elizabeth Van Hook Munson, who had come to the state from Kentucky in 1857. Following three years of study at Valparaiso (Ind.) University, he taught school for three years and began meanwhile the study of medicine with the late Dr. George M. Kreider. He subsequently entered the Northwestern University Medical School and received the M.D. degree in 1893. After several years of practice in Mount Pulaski, he married Miss Daisy North of Rochester, Ill., and went with her to Europe where he attended various clinics in Vienna and studied at the University of Göttingen where, incidentally, his daughter was born. Upon returning to this country, he entered upon his practice of medicine in Springfield, Ill., which continued until a few months before his death. He was a member of the staff of the Springfield Hospital since 1900, and was president of the staff in 1910. From 1936 to 1941 he served as a member of the Medical Advisory Board of the Department of Health of the State of Illinois. In June of 1943, a dinner was held at Springfield in his honor, to mark his completion of fifty years in the practice of medicine, a distinction to which only 290 of the 12,500 physicians in Illinois had then attained. Dr. Munson was a diplomate of the American Board of Internal Medicine.

Dr. Munson received numerous recognitions for his professional work. He was a member and past president of the Illinois State, Central District, and Sangamon County Medical Societies; a member of the Mississippi Valley Medical Society; a Fellow of the American Medical Association. He was also a prominent member of the community as a member of the First Christian Church, as a 32nd degree Mason, past Commander of the Knights Templar; and as a member of the Kiwanis Club.

Dr. Munson became a Fellow of the American College of Physicians in 1922. He rendered distinguished service to the College as Governor for Southern Illinois from 1923 to 1941. He was elected Third Vice President of the College for the year 1941-42.

Dr. Munson was held in great esteem by the members of his profession and all who knew him or of him. A skilled physician, he was very highly regarded for his sincerity and modesty and his deep interest in the young physician who sought his advice when getting started in the practice of medicine. His high ethical standards in life and in the practice of medicine deepen the loss of his passing to his family and the community.

CECIL M. JACK, M.D., F.A.C.P.,
Governor for Southern Illinois

DR. LIONEL SINCLAIR LUTON

Dr. Lionel Sinclair Luton was well known to his colleagues as an inquiring and energetic physician with the personal qualities of a gentleman.

He spent his professional life in St. Louis where he maintained association with the St. Louis Children's Hospital, the St. Louis City Hospital and Washington University for many years. He was particularly active as an Attending Physician at the City Hospital and many men remember him as a sincere teacher during their interne days.

His chief interest was cardiology and he was a member of the St. Louis Heart Association besides of the State and County Medical Societies. He was made a Fellow of the American College of Physicians in 1924.

RALPH A. KINSELLA, M.D., F.A.C.P.,
Governor for Missouri

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PROFESSIO*

By HUGH J. MORGAN, M.D., D.Sc., F.A.C.P., Vanderbilt University
School of Medicine, Nashville, Tennessee

"In nothing do men more nearly approach the gods than in giving health to men."
Cicero: Pro Q. Ligario Oratio.

THE 1948 Class of Fellows and Associates convened here for induction into the American College of Physicians finds itself in troubled times. Three years ago we were quite sure we had seen the end of a global war. With hope, with confidence even, we projected our thoughts into the future. We envisioned the resumption of our accustomed professional activities in a world at peace. We were eager to redeem the personal independence which in the time of national emergency we had gladly placed in pledge to the common cause. Those of us in the federal services desperately wanted a return to home, to friends, to all the old familiar ways of life. No less desperately did those of us in civilian pursuits long for a slackening of war-time tensions, and for the rediscovery of the free choices that characterize normal living. All of us wanted, above everything else, an environment of peace and stability in which to live out our professional careers. That these hopes have not materialized is no longer news. Let the fact serve a purpose, nevertheless, by reminding us that if we are not to replace one set of frustrations with another, we had best reexamine and re-appraise both ourselves and our profession.

Our international relations today are far from peaceful. We hear much of "cold" and "ideological" war. Our leaders in government and the press keep us informed as to what is going on in the world to the end that our country may be prepared for another trial by force if this must come. Regardless of how insane all this appears to be, and how far removed it is from the thoughts and desires of the men, women, and children who must do the dying if war comes again, the fact remains that as yet there is no peace on the international scene.

* Presidential Address, Annual Convocation, American College of Physicians, San Francisco, April 21, 1948.

An examination of the domestic situation is not so depressing but it is far from reassuring. Our economy is in an inflationary spiral and there is no unanimity of opinion amongst the experts either as to the cause of this or the consequences. Even our notions regarding the basic functions of government are not too clear. Here, also, opinion is divided. Social and economic tides are running strong and our little boats of individual judgment are constantly shifting—some of them spinning. Few of us, singly or collectively, are able to steer courses which are precise and in relation to a predetermined direction and objective.

Thus, in 1948, we find ourselves living in a world which is not one world and in a country which misses the cohesion and unity of opinion and action that characterized the war years. That clear and exact focus on objectives which was made possible by an immediate threat to our national existence is no longer obtainable. Of necessity we are forced to bring into our fields of vision many things formerly excluded, and we see them and relate them, one to another, indistinctly and ineffectively. Capital, labor, and agriculture, measuring accomplishment in the main by economic yardsticks, find this post-war period uncertain and perplexing. And so we are living in a difficult, unsettled period. The economists, industrialists, men of business and services, government officials, militarists, tradesmen—all must adjust their activities to this fact. What of the physician?

The propositions of this brief essay are few and quite uncomplicated. They merely assert in one way and another that the physician is more fortunate than many. His character as a member of a profession places him in a more advantageous position in relation to the attainment of his objectives than if he were, so to speak, just a plain member of society. He has both characters, of course, and cannot wholly escape the impact of the distractions, confusions, and uncertainties of these troubled days. But in a sense—a very real and important sense—he, like his fellows in other professions, may have his career and work out his destiny regardless of the times. This is so because his life mission is an unchanging one, not altering either with or after events which profoundly displace and deform the careers and even the objectives of workers in other spheres. This is so, too, because the physician's function in society is of such an importance, quality, and kind, that it cannot be measured by the conventional yardsticks of successful accomplishment, by yardsticks adapted only to the measurement of economic quanta.

This holds true for medicine, I insist, because medicine is a profession. Medicine is neither a business nor a trade. The laws and customs of economics, it is true, do play an essential rôle in the existence of medicine as a profession, as they do in the existence of all organized social forms. But to say that such laws and customs either override the purposes or define the functional operation of the profession is to misconstrue history. True, medical services *do* cost money, and the quality, quantity, and distribution of them *are* tied into economic factors of a most serious and pressing, and often

distressing nature. Nevertheless, I hold that in a democracy these problems are not so much the concern of the professions involved (medicine and its ancillary groups) as they are the concern of the economists and sociologists and statesmen. Professions, because of their very nature, have other and infinitely more important interests. For the profession of medicine the single interest is the safeguarding of the health and the life of the people.

What is a profession? The word is derived from the Latin "professio" which means "open declaration; public avowal; claim, as of a religious faith and purpose." It is defined as "a calling in which one professes to have acquired some special knowledge used by way either of instructing, advising or guiding others or of serving them in some art." The word "calling" is used in the above definition, and it in turn deserves clarification. It is defined, perhaps with an element of mysticism, as "a divine summons, or prompting to a particular act or duty."

Theology, the Law, and Medicine are generally referred to as the three learned professions. They are to be sharply distinguished from Business which "applies especially to occupations of a mercantile nature" and Trade which "applies to any of the mechanical employments or handicrafts except those connected with agriculture."

Dr. Vannevar Bush's concept of a profession as revealed to a group of engineers and recorded in his book of essays called "Endless Horizons"¹ represents the thoughts of a great scientist, a hard-bitten realist, an extraordinary administrator, patriot and one of America's foremost professional men. Dr. Bush emphasizes and reemphasizes the point that the core of a profession is "ministration to the people." The initial and central theme of every one of the professions is that they minister to the people. Ministry is more than just service. It offers no apology and is not subservient. It is characterized by authority based on knowledge. Authority in Medicine implies great responsibility. It follows that dignity and prestige are accorded by the people to those providing this ministration.

Let us turn to the past for a moment and have a view of our medical ancestry, our professional forebears, on this continent. At this meeting in California, the American College of Physicians is reminded of the great pioneer spirit of one hundred years ago which contributed so significantly to the development of the West. Going back still further, Dr. Eugene Bishop, Medical Director of the Tennessee Valley Authority, has something to say about the practice of Medicine in the earliest colonial days in New England, when there were few, if any, educated physicians in America.² Medical services, such as they were, were provided by the preacher and the provincial governor. "The deacon, Samuel Fuller, who came with the Mayflower, rendered medical service as well as spiritual consolation. A little later John Winthrop, the founder of Boston, was administering to the medical needs of his community and, interestingly enough, received from a friend in London—one Dr. Stafford—not only essential advice on therapeutics, but perhaps the first expression of a code of ethics in American Medicine. Said Stafford

in his letter: 'No man can with good Conscience take a fee or a reward before ye partie receive benefit apparent; and then he is not to demand anything that shall be so given him, for it comes from God. A Man is not to neglect that partie, to whom he hath once administered, but to visit him at least once a day, and to meddle with no more, than he can well attend. In so doing he shall discharge a good Conscience before God and Man.' Bishop goes on to say: "We have the obligation to preserve the spirit of the pioneer which so completely dominated the thought of our professional ancestry. If we have in any particular lost the spirit to serve humanity effectively despite every adversity, it must be recaptured as a dominant force in our personal and professional lives. These are pioneer times even though our frontiers are economic rather than geographic. We must place the public good before personal profit now as when Stafford counselled Winthrop to do so." This, you will agree, is a sound, altogether acceptable directive. It is based upon a concept which we acclaim, viz., that Medicine is and must always remain a profession.

Are we practitioners of Medicine in the United States in the year 1948 conducting ourselves in the true spirit of a profession? Obviously, I would not have raised the question if it were not for the fact that I have grave misgivings regarding an affirmative answer. I do not stand alone in this position. Thus, Dr. Bush, a generous critic of "this grand profession," notes: "There is much suspicion in the public mind that aggrandizement, utilization of power for the professional advancement of the membership, the guild spirit in its cruder form, are rampant. . . ." And he admonishes us: "Unless this suspicion is allayed by a revival of simple ideals the profession will suffer, and the people will suffer enormously with it."

There can be no doubt that the industrialization of our country has affected significantly the professional concept in Medicine. In industry success is usually measured in terms of dollars earned. Our clients, who commonly are our intimate friends, often measure our professional stature by the amount of money we earn. Do we? I think many of us do. Is the attitude and practice of physicians less professional and more commercial than it was, let us say, a quarter of a century ago? I am bound to answer, yes. One of our so-called professional organizations has emphasized economics and the material aspects of medical practice so vociferously and forcefully as to lead some of the people and some of the people's representatives in government to consider it a business or trade organization. A Federal Court decision revealed in no uncertain terms that Medicine in the United States, in this instance, forfeited its professional status before the law. It appears that by word and deed we interpreted ourselves to the people and the courts as tradesmen.

Because of the concern I feel for the professional status of Medicine in our country I take especial pleasure in welcoming a group of newly elected Fellows and Associates to membership in the American College of Physicians. This organization is the natural home of the physician who is in

thought and in practice a professional man. In its articles of organization the College defines its mission in simple, clear terms: to maintain and further advance the highest possible standards of medical education, research and practice; to perpetuate the history and best traditions of Medicine and medical ethics; to maintain both the dignity and efficiency of Internal Medicine in relation to the public welfare. An organization with these objectives does, indeed, provide an atmosphere conducive to professional growth and attainment. It is reasonable to hope that through its members it will also help to provide the leadership and guidance requisite for the reclamation and improvement of the professional status of all the clinical branches of Medicine in the United States.

Candidates for Fellowship and Associate Fellowship in the American College of Physicians, you will make a covenant with yourselves and this College in the exercise which follows. Let your recital of the Fellowship Pledge be meaningful and not stilted, empty ritual. This pledge was formulated by our predecessors neither in a spirit of smug complacency nor for purposes of self adulation. Let its recitation, by each of you, constitute a reaffirmation of the ideals and objectives which have come to us through the centuries of medical history—ideals and objectives without which Medicine as a profession does not exist.

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EMETINE TOXICITY IN MAN: STUDIES ON THE NATURE OF EARLY TOXIC MANIFESTATIONS, THEIR RELATION TO THE DOSE LEVEL, AND THEIR SIGNIFICANCE IN DETERMINING SAFE DOSAGE *

By GERALD KLATSKIN, M.D.,† *New Haven, Connecticut*, and HARRY FRIEDMAN, M.D.,‡ *New York, N. Y.*

EMETINE is an important drug in the treatment of amebiasis, even though it frequently fails to cure the intestinal form of the disease. It is indispensable in the management of amebic hepatitis and abscess,¹ it controls the dysenteric symptoms most effectively, and there is evidence to suggest that it improves the end results of treatment in intestinal amebiasis when used in conjunction with other amebicides.² Yet, fear of toxicity has led to the employment of ineffective doses and, in some instances, to the complete abandonment of emetine.²³ There is evidence to indicate, however, that moderate to large doses may be given with safety, provided reasonable care is exercised.¹ Such care, to be effective, must be based on a familiarity with the side-actions of emetine and on an understanding of their significance.

The physiological and structural changes that occur in animals with acute emetine poisoning have been studied exhaustively,³⁻¹³ but comparatively few experiments^{14, 15, 16} have been reported on the effects of chronic poisoning comparable to those seen in man. Most reports of toxicity in man have been concerned with fatal or severely intoxicated cases,^{7, 17-22} or with the more serious cardiovascular,^{23, 24, 25} neuromuscular^{11, 20, 26-30} or gastrointestinal¹⁵ complications of treatment. The early and less severe manifestations of toxicity, so important in the control of therapy, have not received the attention they deserve.

The following investigation was undertaken to determine the nature of the early signs of emetine toxicity, their frequency in relation to dosage and their significance in the control of therapy.

MATERIAL AND METHODS

The subjects were 93 patients in an Army hospital. All but six were males, and, with few exceptions, all were well nourished. The usual indication for emetine therapy was mild intestinal amebiasis. There were two cases of chronic amebic abscess and six of subacute or chronic amebic hepatitis. Several patients received a therapeutic trial of emetine, usually for chronic diarrhea, but occasionally for suspected amebic hepatitis.

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From the Department of Internal Medicine, Yale University School of Medicine.

† Formerly Chief of Medical Service, Schick General Hospital, Clinton, Iowa.

‡ Formerly Chief of Cardiovascular Section, Schick General Hospital, Clinton, Iowa

The subjects were kept at bed rest during the entire period of observation. One grain (.065 gm.) of emetine was administered daily by the subcutaneous route. In a few cases it was given intramuscularly, and in one case six doses were given intravenously. The injections were usually given in the region of the deltoid or gluteal muscles. As a rule the entire daily dose was given in a single injection, but in several patients divided doses were used. Two patients received one-third of a grain daily instead of the usual dose. Several commercial preparations of emetine hydrochloride were employed, some in the form of one-third grain (.022 gm.) soluble hypodermic tablets, others put up in ampoules containing one grain (.065 gm.) of the alkaloid in one cubic centimeter of water.

The total dose used varied from one to 27 grains (.065 to 1.75 gm.). Thirty of the patients received less than 12 grains (0.78 gm.). In seven of these treatment was interrupted by a short rest period, usually three days, after the sixth or ninth dose. Fifty-three patients received 12 grains (0.78 gm.), the course being interrupted by a three day rest period after the ninth grain (0.585 gm.). Ten patients received from 15 to 27 grains (0.975 to 1.75 gm.), with rest periods as indicated below:

Case	Emetine (Grains)	Rest (Days)	Emetine (Grains)	Rest (Days)	Emetine (Grains)	Rest (Days)	Emetine (Grains)	Total	
								Grains	Days
44	5	8	10					15	23
65	9	21	6					15	36
33	9	3	3	19	6			18	40
31	9	3	3	25	7			19	47
32	9	3	3	20	9			21	44
36	9	3	3	26	9			21	50
81	8	4	4	14	9			21	39
82	9	3	3	19	6			21	45
64	9	3	1	14	6	2	3	22	85
4	9	3	3	15	9	46	6	27	57
						12	6		

When the study was planned it was hoped that each of the patients would receive a minimum of 10 grains (0.65 gm.), but treatment was stopped prematurely because of toxic reactions in seven, and because of a variety of other reasons unrelated to the treatment in six others. Two additional patients had to discontinue treatment because of toxic manifestations after 10 to 27 grains (0.65 and 1.75 gm.) respectively. The largest doses were employed in the hepatic amebiasis group.

To ensure the uniformity and completeness of the observations, a printed chart enumerating all the known toxic reactions and the required clinical observations was appended to each patient's record. The medical officer in charge was required to tabulate an entry for each item daily. In addition, each of the patients was seen by one or both authors on several occasions. Any abnormalities noted were described in detail on the back of the special charts, and were graded as mild, moderate or severe.

Since diarrhea was a frequent symptom before treatment, it was not considered a sign of toxicity unless there was a significant increase in severity.

The blood pressure was checked twice daily and the lowest value tabulated. Since the subjects were all bed patients the blood pressure tended to be low before treatment. A fall in blood pressure was considered significant when it fell to 100 mm. Hg systolic and 50 mm. diastolic. In subjects whose initial pressure was below 110 mm. Hg systolic, a fall was not considered significant unless the pressure fell to 90 mm. Hg systolic and 50 mm. diastolic.

The pulse rate was checked a minimum of twice a day and the highest value was tabulated. If the basal pre-treatment rate was under 90 per minute, an increase to 100 or over was considered significant. If the initial rate was between 90 and 100, a rise to 110 or over was considered significant.

Electrocardiograms were taken before treatment and every three days thereafter, at least until treatment was completed, and frequently until all abnormalities had returned to normal. The conventional limb leads and lead C F IV were recorded on a Sanborn Cardiette. Precise measurements of the complexes were made in the usual manner and interpreted by one of us (H. F.).

Many of the patients were observed until all signs of emetine intoxication had subsided, but, unfortunately, it was not always possible to do so. The observations on the duration of toxicity are, therefore, incomplete in many instances.

RESULTS

Incidence of Toxicity. The most striking finding was the frequency with which emetine toxicity occurred. Even excluding the local reaction, which occurred in all but seven patients, no less than 91 per cent exhibited toxic manifestations at some time during treatment. As can be seen in table 1, the signs of toxicity were usually multiple, and in only 20 of the 85 subjects were they confined to a single system.

TABLE I

Summary of Toxic Manifestations Encountered in 93 Subjects Receiving 1 to 27 Grains (0.065 to 1.755 gm.) of Emetine, Exclusive of Local Reactions

	Number	Per Cent
Manifestations limited to one system	20	21.5
Cardiovascular	15	16.1
Neuromuscular	3	3.2
Gastrointestinal	2	2.2
Manifestations in several systems	65	69.9
No toxic manifestations	8	8.6

The individual manifestations of toxicity observed are enumerated in table 2. In general, they fall into four categories: local, gastrointestinal, cardiovascular and neuromuscular, but several, including weakness, headache and dizziness are difficult to classify and have arbitrarily been included in the neuromuscular group. As already mentioned, pain at the site of injection

was experienced by all but a few of the patients. Generalized weakness, electrocardiographic changes and diarrhea occurred in approximately half the subjects, and the incidence of the remaining toxic manifestations varied from 5.4 to 35.5 per cent.

The infrequent occurrence of toxicity observed by others is in striking contrast to these findings. In two large series, in which doses of emetine comparable to our own were employed, the incidence was only 1.4³¹ and 2.8 per cent²⁷ respectively. Even more contradictory are the reports of Heilig and Visveswar³² and Deuskar³³ that they observed no significant toxic manifestations after giving relatively large doses of emetine intravenously.

TABLE II
The Incidence and Duration of Toxic Manifestations during Emetine Therapy

	Incidence		Subsided during Therapy		Subsided after Emetine Was Stopped		
	No.	Per Cent*	No.	Per Cent†	No.	Duration‡ (Days)	Average‡ (Days)
Local pain	86	93.1	23	27.4	63	1-15	4.3
Diarrhea	39	41.9	24	61.5	15	1-14	2.5
Nausea	29	31.2	20	69.0	9	1-5	1.7
E. K. G. changes	49	52.7	7	14.3	42	1-39	9.0
Fall in B.P.	33	35.5	22	66.7	11	1-2	1.2
Precordial pain	33	35.5	17	51.5	16	1-3	1.6
Dyspnea	14	15.0	4	28.6	10	1-5	1.4
Tachycardia	12	12.9	9	75.0	3	1	1.0
General weakness	50	53.7	16	32.0	34	1-25	3.9
"Neuritis"	14	15.0	2	14.3	12	2-30	13.0
Dizziness	9	9.7	4	44.4	5	1	1.0
Headache	9	9.7	5	55.6	4	1	1.0

* Refers to entire series of 93 subjects.

† Refers to the number of subjects exhibiting that manifestation.

‡ Based on incomplete data; in many instances subjects were not followed until last signs of toxicity had subsided.

Relation of Toxicity to Dose. It can be seen from table 3 that signs and symptoms of toxicity appeared as early as the first dose, and, as might be expected with a drug which has a cumulative action,²¹ increased in frequency with the number of doses. The vast majority of toxic manifestations, however, first appeared before the tenth day of treatment. The cumulative effects of emetine are more apparent in table 4, which gives the incidence of toxicity at various dose levels. It should be noted, however, that the increase in toxicity at high dose levels was not striking, nor did it occur with all manifestations. This can probably be related to the rest periods which interrupted treatment.

Duration of Toxicity. Although the action of emetine is undoubtedly cumulative a surprising number of toxic manifestations were transient and subsided in spite of further drug administration. This was particularly true

of nausea, diarrhea, tachycardia, fall in blood pressure and precordial pain, and was least common with the local reaction, electrocardiographic changes, dyspnea, weakness and "neuritis" (table 2). The duration of toxic manifestations following cessation of emetine therapy was quite variable. In general, they subsided in one to three days, except in the case of local pain, electrocardiographic changes and "neuritis" which usually persisted for a week or more (table 2).

In some patients the symptoms were transient in the sense that they occurred shortly after administration of the drug and subsided within a few

TABLE III
Onset of Toxic Manifestations during Emetine Therapy

Emetine Dose, Grains	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
No. Subjects Receiving Dose	93	92	91	90	89	89	89	86	85	78	64	63	10	10	10	8	8	8	7	6	6	2	1	1	1	1	1
Local pain	19	15	12	16	3	6	4	3	6	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Diarrhea	0	5	6	11	4	2	3	2	2	1	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Nausea	3	6	4	5	2	1	1	0	5	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
E.K.G. changes	0	1	3	1	5	1	0	3	16	5	0	13	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Fall in B.P.	0	4	2	8	4	4	0	0	1	5	3	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Precordial pain	3	4	3	5	2	2	4	1	2	1	2	1	1	0	0	0	0	0	1	0	1	0	0	0	0	0	0
Dyspnea	1	0	1	3	0	2	1	2	1	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tachycardia	1	1	0	2	0	1	0	1	2	1	0	0	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0
General weakness	5	3	6	4	3	6	7	4	3	2	3	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
"Neuritis"	0	0	0	2	1	0	0	1	3	0	0	4	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0
Dizziness	6	0	0	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Headache	1	0	1	1	2	1	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Figures in table refer to the number of subjects in whom a toxic manifestation appeared for the first time.

hours, although they recurred with subsequent doses. This was especially true of headaches, dizziness, nausea and precordial pain.

Severity of Toxicity. For the most part the signs and symptoms of emetine toxicity were mild to moderate and showed little tendency to increase in severity. In nine subjects, however, they were sufficiently severe or progressive to warrant cessation of treatment. Multiple toxic manifestations were present in all, but the following were the indications for stopping the drug: precordial pain in three patients after 1, 2 and 9 grains, respectively; persistent electrocardiographic changes in two patients after 9 and 10 grains, respectively; "neuritis" in one patient after 9 grains; fainting in one patient

TABLE IV
The Incidence of Toxic Manifestations during the Course of Emetine Therapy

Emetine Dose, Grains	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
No. Subjects Receiving Dose	93	92	91	90	89	89	89	86	85	78	64	63	10	10	10	8	8	8	7	6	6	2	1	1	1	1	1
Local pain	20	36	48	65	69	72	77	80	79	69	70	64	60	60	70	50	38	63	86	83	83	100	100	100	100	100	100
Diarrhea	0	5	10	20	22	20	20	15	19	17	22	24	20	20	20	25	13	13	14	0	0	0	0	0	0	0	0
Nausea	3	9	10	12	12	12	15	9	14	5	9	8	20	20	20	12	25	12	14	17	17	0	0	0	0	0	0
E.K.G. changes	0	1	4	4	10	11	11	13	26	22	19	38	20	20	40	63	50	50	52	50	67	0	0	0	0	0	0
Fall in B.P.	0	4	3	10	9	11	8	7	12	15	9	11	30	20	30	25	25	25	29	17	17	0	0	0	0	0	0
Precordial pain	4	5	6	7	7	9	11	8	9	6	8	10	10	0	0	0	0	0	29	17	33	0	0	0	0	0	0
Dyspnea	1	0	1	4	2	6	6	6	6	3	8	6	10	10	10	13	13	13	14	17	17	50	0	0	0	0	0
Tachycardia	1	1	1	3	1	2	1	0	1	3	2	2	20	10	20	0	13	0	0	0	33	0	0	0	0	0	0
General weakness	5	4	11	11	16	20	27	27	27	23	26	22	10	10	30	38	38	38	43	50	50	50	0	0	0	0	0
"Neuritis"	0	0	0	2	2	3	2	3	4	5	6	13	10	10	10	13	13	25	43	33	33	50	0	0	0	0	0
Dizziness	7	2	2	1	1	1	1	0	0	3	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Headache	1	1	2	2	5	2	5	6	4	5	5	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

The incidence is expressed as per cent of subjects at any given dose level exhibiting toxic manifestations. It should be noted that these figures do not represent the cumulative incidence of toxicity.

after 3 grains; nausea and vomiting in one patient after 7 grains; and quivering of the muscles and weakness in one patient after 11 grains.

The general plan of treatment was to give 12 grains in 15 days and then shorter courses after rest periods of two to three weeks. In one patient nausea and vomiting occurred after each injection, so that a long period of rest was interposed following the fifth dose. Emetine was then given in one-third grain doses three times a day. Nausea recurred but it was less severe. In two other patients the usual rest periods had to be prolonged because of persistent electrocardiographic changes after 12 and 16 grains respectively. These recurred in one patient when emetine treatment was resumed.

LOCAL REACTION

The local reaction, although never severe enough to warrant stopping emetine, was one of the most troublesome features of treatment. Many patients complained bitterly about it and some were disabled for a week or two after the drug was discontinued.

The reaction was characterized by aching, tenderness, stiffness and weakness of the muscles around the injection site with negligible signs of local inflammation. It usually involved a large area and occasionally spread to the distal portion of the involved extremity. As a rule there was an interval of a day or two between the injection and the onset of symptoms. Quite often a reaction occurred at one injection site but not at others.

The clinical features of the reaction suggested a diffuse myositis rather than the localized subcutaneous inflammatory process frequently seen after the injection of foreign substances. Unfortunately, biopsy specimens could not be obtained. In animals, however, emetine is known to produce extensive capillary hemorrhages in the muscles about the injection site, with little edema and no necrosis.^{14, 34} The same may be true in man.

Urticaria may occur during emetine therapy^{27, 35, 36, 37} and dermatitis may follow direct contact with the drug.³⁸ Neither of these complications was encountered in this series.

GASTROINTESTINAL MANIFESTATIONS

Diarrhea was induced or aggravated by emetine in almost half the subjects. It was frequently accompanied by cramps, but was never severe or associated with blood, mucus or pus in the stools.

Diarrhea is a well recognized sign of emetine toxicity in both man and experimental animals.^{15, 34, 39, 40} It may become so severe that it is mistaken for a dysentery relapse, especially when it is accompanied by blood, pus and mucus in the stools. In animals small doses of emetine administered parenterally increase intestinal peristalsis^{6, 34, 41} while large doses produce edema, congestion and hemorrhages of the mucosa^{12, 14, 15} and occasionally ulceration.^{7, 8, 34} However, no significant changes have been demonstrated in the intestinal mucosa of man.^{7, 17, 18}

The occurrence of diarrhea and cramps without fecal blood, mucus or pus suggests that they were due to increased peristalsis in this series.

Some observers^{8, 34} contend that excretion of emetine into the gastrointestinal tract is an important factor in producing lesions there, but it is doubtful that any significant excretion occurs by that route.⁴⁰ The best evidence indicates that emetine is largely excreted by the kidney.⁴²

Nausea occurred in almost a third of the subjects and was only occasionally accompanied by vomiting. In many it appeared within two hours of an injection and subsided rapidly, but in others it was more persistent.

Nausea and vomiting may be due to the direct action of emetine on the gastric mucosa when it is administered orally,³⁴ but it is doubtful that a direct action occurs when the drug is given parenterally, a possibility suggested by Ghosh and Adhya.⁶ It appears more likely that the drug stimulates the vomiting center either directly⁴³ or reflexly from the viscera.^{6, 43}

The rapid onset and short duration of the nausea noted in many of our subjects was in keeping with a central action, and it may be of significance, in connection with a possible reflex mechanism, that 18 of the 29 had electrocardiographic abnormalities and 13 had diarrhea.

CARDIOVASCULAR MANIFESTATIONS

Cardiovascular manifestations occurred in 77 of the 93 subjects (82.8 per cent), and, as indicated in table 5, were multiple in more than half the

TABLE V

The Interrelations of the Cardiovascular Manifestations Exhibited during Emetine Therapy

	No. Patients	E.K.G. Changes	Fall in B.P.	Precordial Pain	Dyspnea	Tachycardia
E.K.G. changes	49	15*	23	16	8	7
Fall in B.P.	33	23	6*	13	3	2
Precordial pain	33	16	13	10*	9	6
Dyspnea	14	8	3	9	3*	3
Tachycardia	12	7	2	6	3	1*

* No associated cardiovascular manifestations.

group. The following were observed: electrocardiographic changes (52.7 per cent), fall in blood pressure (35.5 per cent), precordial pain (35.5 per cent), dyspnea (15 per cent) and tachycardia (12.9 per cent). None of the patients developed cardiac enlargement or signs of congestive failure. In general the manifestations, except for electrocardiographic abnormalities, were transient and a high proportion of them cleared up despite continued emetine therapy (table 2). The electrocardiographic changes, on the other hand, were of much longer duration and only rarely subsided before emetine was stopped. No patients, however, suffered permanent cardiovascular damage.

In animals, lethal and sublethal doses of emetine produce cardiovascular disturbances which are due primarily to changes in the myocardium.^{5, 7} Sec-

tion of the vagus nerves is without effect in these experiments. Animals that die in less than 48 hours exhibit only interstitial edema of the myocardium, whereas those that survive longer show degenerative swelling and necrosis of myocardial fibers with focal areas of cellular infiltration and interstitial proliferation resembling Aschoff bodies.⁹ Usually there is evidence of cardiac dilatation and congestive failure terminally.^{7, 8, 14} In acute experiments with sublethal doses given intravenously the disturbances of cardiac function produced are very rapidly reversible, and, as far as can be judged from electrocardiographic tracings, leave no residuals.^{4, 5}

There is a wide divergence of opinion regarding the occurrence of myocardial damage following therapeutic doses of emetine in man. Brown,²⁷ reviewing the experience of the Mayo Clinic, found no cardiovascular complications in a series of 554 cases. Included in the group were 25 patients between the ages of 60 and 74 in whom an increased myocardial susceptibility to the drug might be expected. On the other hand, a great number of abnormalities have been observed when serial electrocardiographic studies have been done routinely. Thus, significant electrocardiographic changes were noted in 52.7 per cent of Hardgrove and Smith's⁴⁴ and in 35.6 per cent of Heilig and Visveswar's³² series of patients receiving a total of 10 grains (0.65 gm.) and 12 grains (0.78 gm.) respectively.

Most of the electrocardiographic changes reported have been transient, indicating that the myocardial effects of emetine in therapeutic doses are usually reversible. In several instances, however, evidence of myocardial damage has persisted for many months.^{23, 24} Moreover, degenerative changes in the myocardium have been found in some cases of fatal emetine intoxication.²²

Electrocardiographic Changes. The initial electrocardiograms were considered normal in all cases, except for the following minor deviations: Inversion of T_3 in 13, left axis deviation in six, right axis deviation in two, slurring or notching of QRS_3 in three, and inversion of T_4 in one. Significant abnormalities appeared during treatment in 49 of the 93 subjects (52.7 per cent), and were classified as major in 20, minor in 20, and mixed in 9.

Minor changes included: significant prolongation of the PR interval, but not exceeding 0.20 second, decrease in T-wave amplitude to less than 1 mm., slurring and notching of QRS complexes in a single lead, extrasystoles, and a shifting pacemaker. Prolongation of the PR interval to 0.21 or more seconds, inversion of T-waves, and nodal rhythm were classified as major abnormalities.

As indicated in table 6, the outstanding findings were flattening and inversion of the T-waves and prolongation of the PR interval, which occurred in 24 and 14 cases respectively. Disturbances in rhythm were unusual. One subject developed a transient nodal rhythm with extrasystoles, and two others a few auricular and ventricular extrasystoles. Slurring and notching of QRS_4 occurred in three patients, but no significant changes were noted in the other ventricular complexes, in the ST segments or in the intraventricular

cular conduction time. The maximum PR interval was 0.24 second and there were no dropped beats. Multiple abnormalities frequently occurred in the same patient. Some of these changes are illustrated in figures 1 and 2.

Similar electrocardiographic abnormalities have been observed by others.^{32, 44} When emetine is administered intravenously, changes appear almost immediately, but usually subside in less than an hour. The long-term effects of multiple doses given intravenously, however, are like those described after subcutaneous injections.³² Exercise may aggravate these abnormalities, but it does not precipitate electrocardiographic changes in patients undergoing emetine treatment.³²

TABLE VI

Electrocardiographic Changes Observed in 93 Subjects Receiving Emetine

	No. Subjects	Electrocardiographic Changes	
		Minor	Major
Inversion of P-waves	2*		
P ₁		0	—
P ₂		1	—
P ₃		2	—
Prolongation of PR interval	14	3	11
Slurring and notching QRS ₁	3	3	—
T-wave changes	36*		
T ₁		17	1
T ₂		15	5
T ₃		0	15
T ₄		13	10
Changes in rhythm	4		
Auricular extrasystoles		1	—
Ventricular extrasystoles		1	—
Nodal extrasystoles		1	—
Nodal rhythm		—	1

* Multiple abnormalities account for the discrepancy between the number of subjects and the number of E.K.G. changes. Of the 36 subjects with T-wave changes, 17 had minor, 13 major and 6 both types of abnormality.

Recently Dack and Moloshok²⁵ have reported that electrocardiographic changes may not appear until a week or two after emetine therapy is discontinued. This possibility was not explored in the present investigation, although it can be expected that no electrocardiographic abnormalities present at the end of treatment, increased after the drug was withdrawn.

Heilig and Visveswar³² observed that many of their patients exhibited electrocardiographic abnormalities before treatment and that a high proportion of these reverted to normal under the influence of emetine. In the present series the only change of this kind noted was the return of an inverted T₃ to the upright position in three subjects.

Much more striking electrocardiographic changes have been reported in experimental animals,^{4, 5, 10} due, no doubt, to the relatively large doses of emetine and the intravenous route of administration usually employed. In acute experiments with a single sublethal dose recovery occurs in less than an

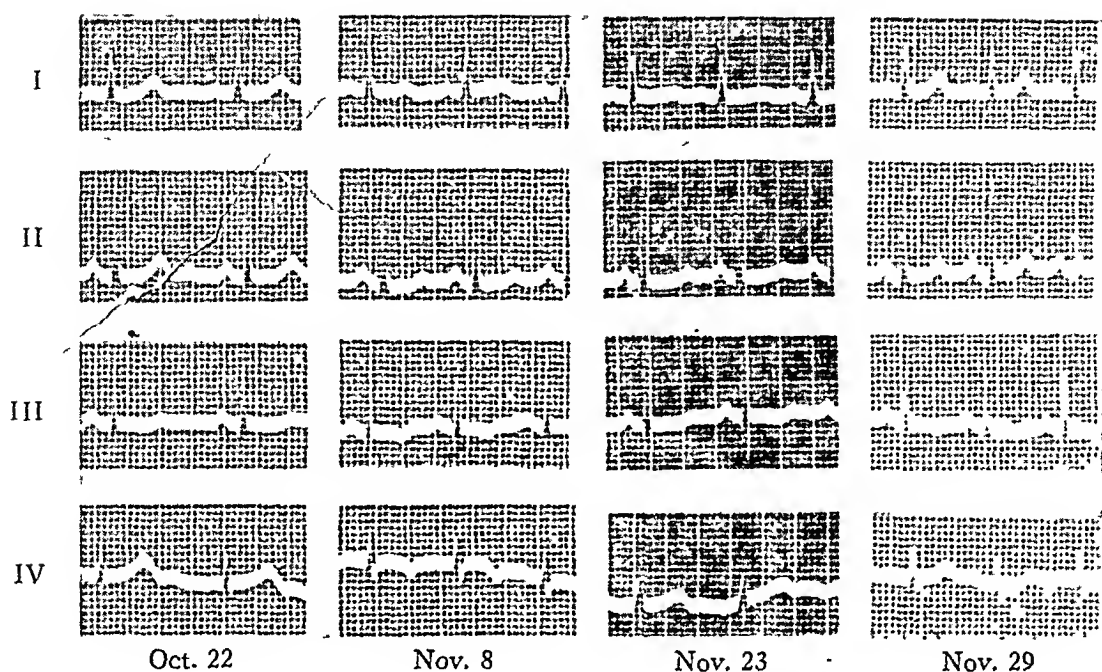


FIG. 1. Case 64. Typical T-wave changes after emetine treatment. October 22: normal E.K.G. before treatment. November 8: inversion of T_2 and T_3 after 10 grains (0.65 gm.) of emetine. November 23: return to normal after 15 day rest period. November 29: inversion of T_2 after 6 more grains (0.39 gm.) of emetine.

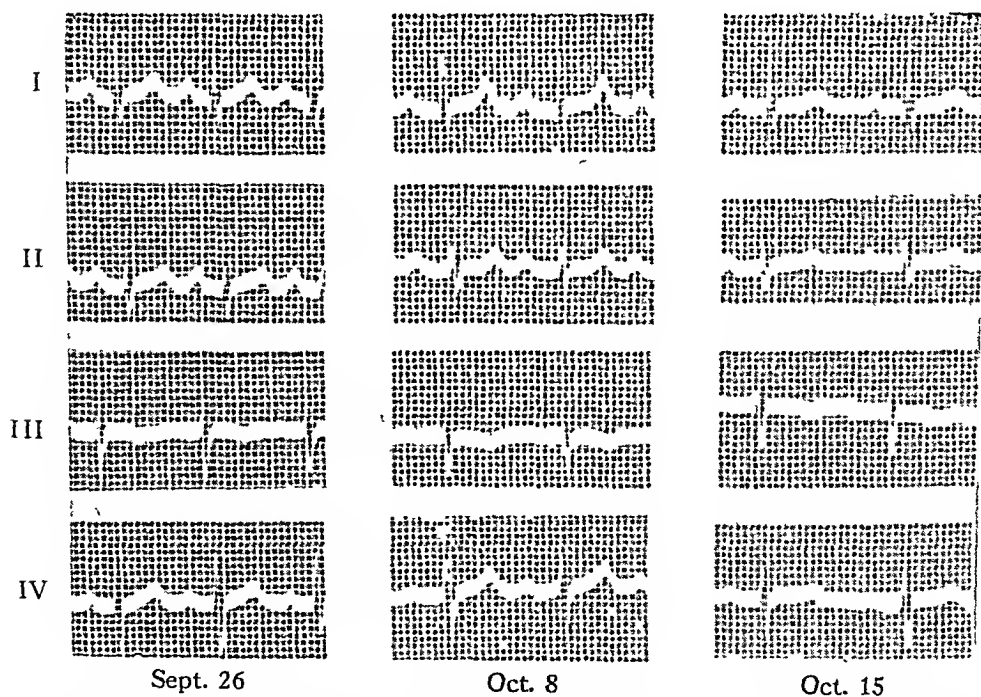


FIG. 2. Case 29. Prolongation of PR interval after emetine treatment. September 26: PR 0.20 second before treatment. October 8: PR 0.24 sec. after 9 grains (0.585 gm.) of emetine. October 15: PR 0.20 second after nine day rest period.

hour. The principal abnormalities that appear are intraventricular and auriculo-ventricular block, inversion of T-waves and disturbances of rate and rhythm. Dropped beats and complete heart block occur in cats but not in dogs. Bradycardia is usually present early, but may be replaced by tachycardia if a disturbance of rhythm occurs. Auricular extrasystoles are common and may be succeeded by auricular tachycardia. Ventricular extrasystoles and ventricular tachycardia occur much less frequently and may go on to ventricular fibrillation. Acutely lethal doses of emetine produce either ventricular fibrillation or idioventricular rhythm with progressive slowing and ultimate diastolic standstill.⁵ Vagus section⁵ and digitalis⁴ have no effect on these changes.

Tachycardia is a common sign of emetine toxicity in man, but only rarely are other disturbances of rate and rhythm encountered. Marked bradycardia has occurred after very large doses given intravenously²¹ and transient auricular fibrillation has been observed after multiple small doses given subcutaneously.²⁴

Hypotension. A significant fall in blood pressure occurred in about a third of the patients (table 2). The systolic pressure usually fell 15 to 20 and the diastolic 5 to 10 mm. of mercury. The lowest pressure recorded was 82/48 in a subject whose pretreatment pressure was 96/54 mm. Hg.

The hypotension associated with emetine administration may be due to several mechanisms. In experimental animals receiving relatively large doses intravenously it appears to be due to a direct action on the myocardium.^{6, 8, 10} Even under these conditions, however, there is some evidence to indicate that emetine may act directly on the blood vessels causing vasodilatation⁴¹ or on the vasomotor center leading to a fall in blood pressure.⁶ In animals, at least, vasovagal reflexes do not appear to be a significant factor, since section of the vagus nerves does not alter the hypotensive effects of emetine.^{6, 7, 8} Other reflex mechanisms mediated through the vasomotor center, however, have not been excluded.

In man there appears to be very little relationship between the hypotensive and myocardial effects of emetine.³² In the present series approximately two-thirds of the subjects with hypotension exhibited electrocardiographic abnormalities (table 5), but in no instance did they indicate myocardial damage severe enough to account for a fall in blood pressure. Furthermore, none of the subjects developed cardiac dilatation or congestive failure, complications that might be expected under those circumstances. It seems probable that the hypotension that occurs in man following therapeutic doses of emetine is due to its action on the vasomotor center, either directly or reflexly. The rôle of the vagus in this mechanism has not been studied in man. The immediate fall in blood pressure and the evanescent electrocardiographic changes that occur following intravenous injections³² are highly suggestive of vagal effects. The factor of vasodilatation has not been investigated in man, but the striking absence of tachycardia in the present group of hypotensives (table 5) suggests that it cannot be of primary importance. The

epinephrine content of the adrenal gland is lowered by emetine⁴⁵ and Leibly's case of fatal emetine poisoning exhibited degenerative changes in the adrenals,¹⁸ but there is no convincing evidence that the adrenals play any rôle in emetine hypotension.

Precordial pain occurred in a little over a third of the patients (table 2). It was usually mild to moderate in severity, aching in character and poorly localized in the region of the left nipple. In several patients it was sharp and shooting in character and could be increased by movement in bed. Two subjects noted the pain a half hour after each injection. The pain did not radiate to the shoulders or arms in any of the patients.

The significance of this symptom was difficult to evaluate. It had none of the usual characteristics of coronary pain, although the associated cardiovascular abnormalities occasionally suggested it (table 5). However, there is no evidence that the coronary vessels are adversely affected by emetine. Even spasm would appear to be excluded by the demonstration that emetine increases coronary blood flow.¹⁰ It is conceivable that significant myocardial lesions might give rise to pain. Hardgrove and Smith⁴⁴ encountered precordial pain in one of their patients. The T-wave changes suggested coronary occlusion, but there were no other electrocardiographic, clinical or laboratory signs of myocardial infarction. According to Chopra and Ghosh³⁴ three of Hall's cases experienced constriction in the chest before death, and showed marked myocardial degeneration at autopsy. In the present group, however, the electrocardiograms were either normal or indicated only minor injury to the myocardium.

Dyspnea occurred in 14 of the 93 subjects. It was a purely subjective complaint and was not accompanied by a significant increase in the respiratory rate. Although it was frequently associated with other cardiovascular manifestations (table 5), the infrequent occurrence of tachycardia and the absence of cardiac enlargement, pulmonary congestion and venous engorgement cast doubt on the cardiac origin of the dyspnea. Generalized weakness, on the other hand, occurred in all but two of these subjects, so that the dyspnea may have been related to it rather than to cardiac failure.

Heilig and Visveswar³² were unable to demonstrate any functional incapacity of the heart by an exercise tolerance test during the course of emetine therapy, even when definite electrocardiographic abnormalities were present. However, several fatal cases have been reported^{17, 18} in which dyspnea was probably due to myocardial injury and failure.

It seems fair to say, then, that the dyspnea associated with emetine therapy is frequently not cardiac in origin, although it may be so under some circumstances.

Tachycardia is sometimes considered one of the early signs of emetine toxicity,⁴⁶ yet, in the present study it was the least common of the cardiovascular manifestations (table 2). However, had the patients been allowed up and about, as recommended by Cawston,⁴⁶ tachycardia might have occurred earlier and more frequently.

The mechanism by which tachycardia is produced has not been worked out in man. It has been suggested that it is due to the effects of emetine on the myocardium,^{14, 32} the vagus nerves³⁰ and the intracardiac nerve endings.⁴⁶ As can be seen in table 5, only five of the 12 subjects with tachycardia exhibited abnormalities in the electrocardiogram, so that a primary myocardial effect is unlikely. The tachycardia cannot be related to a fall in blood pressure since hypotension occurred in only two subjects. Unfortunately the rôle of the neurogenic mechanism was not investigated. Although a general myocardial effect did not appear important, it is quite possible that the tachycardia is due to the effect of emetine on the sinoauricular node.

In summary, then, cardiovascular manifestations were common during emetine therapy, and although many subjects developed electrocardiographic abnormalities indicating myocardial damage, there was evidence to suggest that the other signs and symptoms were usually not myocardial in origin.

NEUROMUSCULAR MANIFESTATIONS

More than half the group exhibited signs and symptoms which were classified as neuromuscular (table 2). So many of these were associated with gastrointestinal and cardiovascular manifestations (table 1), however, that it was not always possible to be certain of their neuromuscular origin.

Weakness was one of the most common signs of emetine toxicity encountered. It was a purely subjective complaint and many patients had difficulty in describing it. In some it appeared to be muscular, although no weakness or tenderness of the muscles could be demonstrated, while in others it was expressed as listlessness and unusual fatigability.

As a rule the weakness developed insidiously and lasted for several days. In many instances, however, it was present intermittently. Transient weakness, within an hour or two of an emetine injection, occurred in five subjects. In none of these was there any fall in blood pressure and only two exhibited tachycardia and one a change in the electrocardiogram. One subject developed generalized muscular weakness associated with coarse tremor, quivering of the muscles and nervousness shortly after his eleventh dose of emetine (0.715 gm.). These lasted eight hours and the following morning there was a brief recurrence although no more emetine was administered.

Weakness has not received much attention as a sign of emetine toxicity, although it has been recognized before both in man^{17, 27} and in experimental animals.³ Its pathogenesis is quite obscure, but it has been suggested that it may represent a mild form of emetine "neuritis".²⁷ Certainly this possibility seemed reasonable in some of the present group, especially in those that subsequently developed "neuritis," but in others no adequate explanation could be found. Gastrointestinal and cardiovascular manifestations occurred so irregularly in the group (table 7), that they could hardly have been of primary importance in producing weakness.

TABLE VII
Relation of Neuromuscular to Other Manifestations of Toxicity

	Sub- jects	Diarrhea	Nausea	E.K.G. Changes	Fall in B.P.	Record Pain	Dysp- nea	Tachy- cardia	Gen'l Weak- ness	Dizzi- ness	No Other Signs
General weakness	50	18	17	23	9	15	10	4	50	0	13
"Neuritis"	14	6	3	7	2	2	3	2	12	0	2
Dizziness	9	0	6	2	3	2	1	2	6	9	0
Headache	9	2	2	5	3	1	3	0	4	2	1

"*Neuritis.*" Fourteen subjects developed a syndrome which is commonly regarded as "emetine neuritis." As indicated in table 8 the outstanding features were bilateral weakness, pain, tenderness and stiffness of the extremities and neck. The calves and forearms were the regions most com-

TABLE VIII
Clinical Features of Emetine "Neuritis"

Case No.	Day of Onset*	Dura- tion Days	Location	Muscle Weak- ness	Pain	Muscle Tender- ness	Muscle Stiff- ness	Pares- thesia	Sensory Loss	Dimin- ished Reflexes
18	4	4	Neck	0	+	0	+	0	0	0
48	4	10	Arms, legs	+	0	0	0	0	0	0
34	5	30	Neck	+	+	0	0	0	0	0
19	8	2	Neck	0	+	0	0	0	0	0
44	10	14	Arms, legs	+	0	0	0	0	0	0
46	10	3+	Legs	+	0	0	+	0	0	0
80	10	25	Arms, legs, shoulder, back	+	+	+	+	0	0	0
7	2 days after 12	7	Calves	0	+	0	+	0	0	0
49	6 days after 12	10	Arms, legs	+	+	+	+	0	0	0
50	6 days after 12	7	Legs	+	+	+	+	0	0	0
51	2 days after 12	7	All muscles esp. calves	0	0	+	+	0	0	0
31	18	21	Legs	+	+	+	0	+	+	0
36	19	21	Calves	+	+	+	0	+	+	0
64	7 days after 16	21	Calves	+	+	+	0	+	0	0

* Refers to days of treatment, or grains of emetine.

Case 31 had had paresthesia and numbness intermittently since an attack of frost-bite 9 months before emetine treatment.

Case 36 had had severe peripheral neuritis due to malnutrition 4 months before emetine treatment.

monly affected. Muscular weakness varied in severity, but was usually only moderate in degree. In one subject (Case 50), however, it was severe enough to interfere with walking, and in another (Case 34) the head could not be held erect. The pain was aching in character and poorly localized in large muscle groups, and, except in one instance (Case 36), had none of the lancinating quality or characteristic distribution of neuritic pain. Half the group had muscle tenderness, and a similar number complained of stiffness, but none of the subjects exhibited muscular atrophy, spasticity or fibrillation, tenderness of the peripheral nerves or diminution of reflex activity. Only three of the 14 subjects had a sensory disturbance. The first (Case 31) complained of numbness and exhibited mild hypoaesthesia and hypalgesia of the hands and feet. These were noted during the initial examination, but according to the patient, they had been present intermittently for nine months, since an attack of frost-bite. The second (Case 36) developed shooting pain in the legs associated with weakness and tenderness of the calves and slight hypoaesthesia and hypalgesia of the feet. He had been a prisoner-of-war for a long period of time and had suffered from severe malnutrition. Four months before the institution of emetine treatment he had developed a severe peripheral neuritis of the legs. This had subsided under vitamin therapy and had not recurred until emetine was administered. The third patient with a sensory disturbance (Case 64) developed paresthesia but never exhibited any loss of sensation.

In addition to these three patients in the "neuritis" group, there were four others who developed mild paresthesia which lasted from one to three days. In none of the latter was there any demonstrable loss of sensation, change in the reflexes, pain, tenderness or muscular weakness. The paresthesia subsided despite the continuation of emetine treatment in three of the four patients.

A number of subjects with severe local reactions noted pain in the distal portion of the involved extremity. In many respects their signs and symptoms resembled those of emetine "neuritis." An unusual feature of emetine "neuritis" was the occurrence of a latent period between the cessation of drug therapy and the appearance of symptoms. This occurred in five patients and varied from two to seven days in duration (table 8). Another feature was the unusually long duration of the symptoms following withdrawal of emetine, averaging two weeks (table 2).

Numerous cases of emetine "neuritis" have been reported,^{16, 17, 20, 26, 27, 29, 30, 40, 42} but not nearly as many as might be expected considering the widespread use of the drug and the relatively high incidence of this complication in the present study. On the whole the reported cases have been much more severe than those described here. Muscular weakness has often progressed to actual paralysis with foot-drop,^{16, 29} wrist-drop,²⁹ and inability to hold the head erect.¹⁷ In a few instances the muscles of deglutition and respiration^{17, 20} have been involved. Death has occurred in some of these cases,¹⁷

but usually there have been so many other toxic manifestations that it has not been possible to assign the cause of death precisely.

Emetine "neuritis" has usually occurred after doses exceeding 15 grains (1.0 gm.), but it has also been reported after as little as 3 to 6 grains (0.195 to 0.390 gm.).³⁰ The relatively long duration of the "neuritis" is well recognized,^{16, 29} although occasional cases¹⁷ have subsided in less than two weeks. The latent period between the cessation of treatment and the onset of symptoms has been noted by others.^{16, 27, 29} It will be recalled that a similar latent period occurs occasionally before the onset of electrocardiographic abnormalities.²⁵

Many features of the "neuritis" syndrome observed in the present study and described in the literature suggest that it is usually due not to a disturbance of the nervous system, but rather to a primary disorder of the muscles, probably a myositis. If a true emetine neuritis, in the sense of a demonstrable inflammatory or degenerative lesion of the nerves, does occur it must be quite rare. The usual signs of neuritis, namely, loss of reflexes, disturbances of sensation and muscular atrophy have usually been absent in the cases reported both here and elsewhere. Only occasionally have diminished reflexes,^{16, 30, 42} sensory loss²⁰ and muscular atrophy¹⁶ been observed. The only two patients with definite sensory loss in the present series had had signs of neuritis before emetine was administered. It is quite possible that emetine precipitated a relapse of a preëxistent neuritis in these cases. Five other subjects complained of paresthesia, but the short duration of the symptoms and the absence of objective neurological signs were strongly against a neuritic etiology. The tenderness and the pain, on the other hand, which were such striking features of the syndrome, were definitely localized in the muscles, rather than along the nerves, suggesting a myositis.

Young and Tudhope¹⁶ were able to produce weakness of the hind limbs in rabbits and guinea-pigs with repeated small doses of emetine, and found degenerative changes in the muscles, anterior horn cells and the motor fibers of the peripheral nerves. There were no inflammatory lesions in the nerves or their sheaths. By the time neural degenerative changes appeared, injury to the other organs was so far advanced that recovery seemed doubtful. They concluded that the paralysis seen after emetine administration in man, which is usually reversible, is due to the direct action of the drug on the muscles. Paralysis has been observed occasionally in other experiments,^{3, 8, 29} but in none have histologic studies of the nervous system been carried out. Kilgore and Liu¹⁵ attempted to produce emetine neuritis in the dog, but were unable to find any changes in the nervous system. Anderson and Leake³ noted hyperemia and hyalinization of muscles, but did not examine the nerves. Young and Tudhope's experiments differ from all the others in that much smaller doses were employed over a long period of time. It may be that in more acute experiments death occurs before neurologic changes can develop.

Manson-Bahr³¹ and Napier⁴⁷ state that emetine may produce both neuritis and myositis in man. Unfortunately there are no autopsy or biopsy reports to confirm this view. All that can be said at present is that clinical observations and experimental studies suggest that the "neuritis" syndrome following emetine is usually due to a myositis, but that peripheral neuritis may occur under some circumstances.

Dizziness or faintness was noted in nine subjects. In seven of these it occurred shortly after an emetine injection and subsided in a few hours. In the remaining two it was noted when the patient attempted to get out of bed.

Three of the subjects had definite attacks of faintness. In the others the symptoms suggested mild vertigo. Case 23 complained of nausea and weakness for two hours after each injection of emetine. Following the third he fainted, and later claimed to have been unconscious for an hour. He was not observed during this period, but a few hours later he appeared perfectly normal. Case 60 developed precordial pain and faintness after his first injection and emetine treatment was stopped. The reaction was thought to be hysterical since there was no change in the vital signs and since the same reaction followed a venapuncture two days later. Case 63 experienced faintness, profuse sweating and tachycardia after his first injection. The electrocardiogram was normal. The symptoms lasted 20 minutes and did not recur following the next 11 injections of emetine.

The data, presented in table 7, do not warrant any definite conclusion regarding the pathogenesis of these symptoms. Cardiovascular abnormalities occurred so infrequently in this group, it is unlikely that they were an important factor in producing faintness and dizziness. Nausea, on the other hand, occurred in six of the nine subjects. Nausea not infrequently is accompanied by faintness and dizziness, so that it may have been of importance in this group. It is of interest that these symptoms occur with some regularity after intravenous injections of emetine and that they are more commonly associated with nausea than with cardiovascular phenomena.^{21, 48}

Headache. Nine subjects developed headache several hours after emetine was administered. In six of these it occurred with such regularity after repeated doses, it seems reasonably certain that it was due to the drug. An analysis of the associated symptoms and signs (table 7), however, offers no clues as to the nature of the headaches. It is quite possible that intracranial vasodilatation due to emetine was an important factor.

Other Visceral Manifestations of Emetine Toxicity. Lethal doses of emetine produce degenerative changes and congestion in the liver and kidneys of experimental animals.^{3, 7, 8, 12} Some of these are undoubtedly secondary manifestations of cardiovascular failure. Similar changes have been described in man.^{7, 18}

The kidneys and liver were not investigated routinely in the present study. Nevertheless, most of the subjects had urine specimens examined either during or after their course of emetine. No abnormalities that could be attributed to the drug were noted. The patients with proved or sus-

pected hepatic amebiasis had elaborate studies of liver function. Abnormalities were noted in some, but these returned to normal under the influence of emetine.

COMMENT

The data presented clearly indicate that mild toxic manifestations are common during emetine therapy and may occur at any dose level. The relatively low incidence of toxicity reported by others^{27, 31, 33} has usually occurred in studies not primarily concerned with emetine toxicity. It is noteworthy that investigations designed to demonstrate the early signs of toxicity have usually revealed a number comparable to those reported here.^{32, 44}

Some observers⁷ have attempted to demonstrate differences in toxicity among commercial preparations of emetine. The careful studies of Lake,¹² however, show clearly that these differences are due to marked variations in individual susceptibility to the drug.

Emetine appears to be a general protoplasmic poison with a special predilection for muscle and, possibly, nerve tissue, not only of the heart, but also of the vascular, gastrointestinal and skeletal systems. It is not surprising, then, that multiple manifestations are so common once toxicity occurs. Emphasis on the cardiac and neuritic effects of emetine has tended to divert attention from the others. Necropsy studies on both man and experimental animals amply confirm the multiplicity of lesions produced by emetine.

The fatalities that have resulted from emetine have almost invariably been preceded by easily recognizable signs of toxicity.^{7, 17, 18} It is important, therefore, to answer the question of whether further emetine treatment is safe once the early signs of toxicity appear.

It is evident from the data presented that many of the toxic manifestations subside even when treatment is continued, suggesting that, within limits, a degree of tolerance to the drug may be acquired, and that some of the manifestations, at least, may be due to tissue changes that are rapidly reversible. Emetine "neuritis" and electrocardiographic abnormalities, on the other hand, show little tendency to regress unless treatment is stopped, and probably reflect much more serious and less easily reversed tissue changes. The appearance of either of these complications is, therefore, an indication for immediate cessation of emetine therapy. The occurrence of other toxic manifestations, if mild, should alert one to the possibility of more serious consequences, but need not contraindicate further treatment unless they show a tendency to increase in severity or fail to subside within a day or two.

Large doses of emetine are frequently required in the management of amebiasis of the liver¹ and occasionally a second course of emetine is indicated in intestinal amebiasis. In both instances therapy must be interrupted by appropriate rest periods to compensate for the well-recognized cumulative effects of the drug. The length of the periods compatible with safety has

not been worked out precisely, although a number of suggestions have been offered.^{34, 40} The intervals chosen in the present study appear to have been satisfactory, since no serious ill effects were encountered following relatively large doses of emetine. An attempt was made to standardize the rest periods between courses, but experience proved the necessity for modifying the basic outline in many cases after careful consideration of the type, severity and duration of the toxic manifestations.

The local reaction to emetine is one of the most troublesome features of treatment. According to Brown²⁷ and others⁴⁰ it can be minimized by injecting the drug subcutaneously rather than intramuscularly. The subcutaneous route was employed almost exclusively in the present study, but disabling pain and tenderness were common. Cawston⁴⁶ recommends the intramuscular route and suggests that the addition of 1 per cent carbolic lotion will prevent the reaction. The use of any local anesthetic would appear to be futile, since the reaction usually occurs at least 24 hours after the injection.

The intravenous and oral routes of administration offer a number of advantages including the avoidance of a painful local reaction. Unfortunately, there are practical and theoretical objections to both.

Most workers^{7, 11, 34} agree that the intravenous route is too dangerous for general use, although it may be employed under special circumstances. This opinion is largely based on the fact that the toxicity of emetine is very much greater by this route than by any other, as judged by the minimal lethal dose in animals.^{10, 40, 50, 51} Nevertheless, in the therapeutic range intravenous emetine has not proved to be more toxic in man, although transient immediate reactions have been much more frequent.^{21, 32, 33, 48} The rapidity of the injection and the dilution employed may be important factors in determining these immediate reactions.^{7, 11, 12}

Sudden death, usually due to ventricular fibrillation, occurs quite commonly in animals following intravenous injections of emetine.^{4, 5, 7} This reaction has not been reported in man, although it may have occurred in Stern's case,¹⁹ and the dose required to induce it in animals is larger than that generally employed therapeutically. Nevertheless, it is a distinct hazard, especially as there is so much variability in individual susceptibility to the drug. The discomfort of the local reaction does not appear to be serious enough to warrant the added risk of intravenous therapy.

Orally administered emetine is well absorbed from the upper gastrointestinal tract⁴⁰ and is effective therapeutically,⁵² but nausea, vomiting and diarrhea are so common, even when the drug is coated with keratin or salol, that it is seldom used. Recently, Shrapnel and his associates⁵² have reported that relatively large doses are well tolerated if the emetine is sealed in a material designed to withstand digestion for three or four hours. Few of their patients developed gastrointestinal symptoms and none exhibited signs of toxicity, even after doses as large as 23 grains (1.495 gm.) given over a 19 day period. The authors attribute this unusual resistance to toxicity to a relatively slow absorption from the distal portion of the small intestine and

colon, where, presumably, the drug is released. In other studies³ emetine has proved to be as toxic by the oral as by the subcutaneous route, although in none of these experiments was absorption from the distal portion of the intestinal tract investigated. The excretion rate of emetine, however, is so slow⁴² it is doubtful that absorption can be retarded sufficiently to overcome its cumulative effects. Furthermore, a report from the pharmaceutical laboratory which prepared the emetine tablets which Shrapnel used states that with more extensive experience distressing gastrointestinal symptoms have been encountered.⁵³ In spite of these conflicting reports, Shrapnel's results are so unusual that his method deserves further investigation.

Most workers^{25, 34, 54} recommend bed-rest for patients undergoing emetine treatment. A few^{40, 55} allow their patients to continue their usual activities. Although no definite evidence has been advanced to prove the ill effects of exercise, the high incidence of electrocardiographic abnormalities suggesting myocardial damage during emetine treatment warrants the same precautions accorded other forms of myocarditis.

The latent period that occurs occasionally between the withdrawal of emetine and the appearance of "neuritis" and electrocardiographic changes calls attention to the necessity for keeping patients under observation following treatment, and illustrates the danger of judging drug tolerance solely on the basis of the electrocardiogram. Fortunately the other signs of toxicity usually appear earlier and make it possible to avoid serious overdosage.

There is some difference of opinion regarding the advisability of using emetine in the face of organic heart disease. Mackie⁵⁷ warns against it. Heilig and Visveswar,³² on the other hand, do not consider the presence of electrocardiographic abnormalities a contraindication. One of our abscess cases, not included in the present report, exhibited marked left bundle branch block of undetermined etiology. He was given very large doses of emetine, without any significant change in his electrocardiogram or in his cardiovascular status. The evidence is inconclusive, but it seems probable that there is an added risk in using emetine in the presence of organic heart disease, particularly when it is accompanied by myocardial failure or a disturbance in conduction or rhythm. The decision to use emetine under these circumstances must rest on the urgency of the need for emetine. If it is great, as in acute amebic abscess, the risk must be accepted, but it can be minimized by careful observation for signs of toxicity and, in some instances, by reducing the daily dose.

Little is known about the fundamental changes that emetine produces in protoplasm. The only pertinent studies are those of Meyer and Williams⁵⁸ who demonstrated a decrease in blood carbon dioxide and those of Pellini and Wallace⁸ who found an increase in urinary nitrogen after emetine. These changes, which have been interpreted as indicating a disturbance of intracellular oxidation, are also produced by other poisons, like arsenic and phosphorus.

SUMMARY AND CONCLUSIONS

1. Toxic manifestations are common in the therapeutic dose range of emetine, and may occur at any dose level depending on individual susceptibility to the drug.

2. Emetine is a general protoplasmic poison with a predilection for muscle, and possibly nerve, tissue, not only of the heart, but also of the vascular, gastrointestinal and skeletal systems. This is reflected in the multiplicity of manifestations that appear once toxicity occurs.

3. The manifestations of emetine toxicity fall into four groups: local, gastrointestinal, cardiovascular and neuromuscular.

4. The local reaction occurs in all but a few patients when emetine is given subcutaneously. Generalized weakness, electrocardiographic changes and diarrhea occur in approximately half the subjects, and the incidence of the other toxic manifestations varies between 5.4 and 35.5 per cent.

5. The local reaction appears to be due to a myositis in many cases.

6. The diarrhea induced by emetine is due to increased peristalsis. With very large doses ulceration of the mucosa may occur, although this has never been demonstrated in man. The nausea and vomiting are probably of central origin when the drug is given parenterally.

7. Emetine produces changes in the myocardium, as evidenced by the appearance of electrocardiographic abnormalities, but the other cardiovascular manifestations of toxicity seen in man are usually not cardiac in origin.

8. The clinical features of emetine "neuritis" are usually those of a myositis. If a true emetine neuritis occurs in man it must be rare.

9. Although the effects of multiple doses of emetine are cumulative, many of its toxic manifestations subside during treatment, suggesting that some degree of tolerance may be acquired. Electrocardiographic abnormalities and "neuritis" rarely regress unless treatment is stopped, so that their appearance is an indication for immediate withdrawal of emetine. The other signs of toxicity, however, need not contraindicate further treatment unless they increase in severity or fail to subside in a day or two.

10. The toxic effects of emetine are reversible if the drug is stopped early enough. Most of them clear up in a few days, but electrocardiographic changes and "neuritis" may persist for weeks.

11. There may be a latent period between the cessation of emetine therapy and the appearance of electrocardiographic abnormalities and signs of "neuritis." Patients should, therefore, be kept under observation for several weeks following treatment.

12. Relatively large doses of emetine can be given with safety, provided treatment is interrupted by rest periods adequate to compensate for the cumulative effects of the drug.

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EXPERIENCE WITH THE SCHEMM REGIMEN IN THE TREATMENT OF CONGESTIVE HEART FAILURE *

By ABBOTT A. NEWMAN,† M.D., and HAROLD J. STEWART, M.D., F.A.C.P.,
New York, N. Y.

THE introduction of the mercurial diuretics has been one of the great advances in the treatment of heart failure in recent years. This, coupled with the demonstration of safe rapid therapeutic digitalization and the adequate maintenance use of digitalis has prolonged the productive activity of patients with heart disease and has increased their life span. For many years restriction of salt and fluid intake has been accepted as a beneficial practice in the treatment of cardiac failure. The importance of the limitation of salt in controlling edema was again emphasized by Schroeder¹ in 1941. Proger, Ginsberg and Magendantz² in 1942 concluded that the harmful effects of an increased intake of salt were due to the retention of sodium. Schroeder¹ was of the opinion that large amounts of fluid could be taken without the production of edema or accumulation of fluid provided the intake of salt was kept at a low level. Application of this principle was made by Schemm^{3,4} in the treatment of congestive heart failure in a regimen which stressed a very high daily fluid intake and a diet which was low in sodium and yielded a neutral or acid ash residue.

Schemm's observations,^{3,4} prompted us to test this method of treatment and to ascertain first, if it was effective and, secondly if its use was accompanied by advantages over other current methods. Our experience forms the basis of the observations now to be reported.

METHODS

Patients with congestive heart failure were admitted to the hospital for this study. No selection was made with respect to the etiology of the cardiac disease. Patients with detectable amounts of fluid accumulations, such as edema, ascites, or pleural effusion, lent themselves to the study most easily. In only nine of 30 patients under observation were the data satisfactory for analysis. In the remaining 21 cases lack of coöperation, complete disappearance of edema during a period of control, or complicating factors, such as diabetes, infection, or severe pulmonary edema made the data analytically unsuitable.

On admission all patients were observed during a preliminary control period before institution of the Schemm regimen. During this time they

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From the Department of Medicine of the New York Hospital and Cornell University Medical College, New York, New York.

† Volunteer Fellow, Department of Medicine (Cardiology), 1946 to 1947.

were put at complete rest in bed, given a three gram salt diet, a fixed daily fluid allowance, usually 1200 c.c., and maintenance amounts of digitalis. Patients were digitalized when it was thought advisable. Mercurial and other diuretics were not administered unless absolutely necessary. Thoracenteses and paracenteses were performed only to relieve severe discomfort. The weight was recorded daily before breakfast after the bladder was emptied. The total fluid intake and output were measured each day. In some the pH and the specific gravity of the urine were measured every day and in others, every other day, usually in the afternoon during the so-called "alkaline tide." The serum proteins, venous pressure, circulation time, plasma CO₂ and chlorides, hematocrit and other data were obtained in certain patients.

The preliminary control period was maintained (1) until the weight stabilized and there was little apparent change in the clinical condition or (2) until a rising weight curve and increase in fluid accumulation indicated that no benefit was being derived from the management. The regimen outlined by Schemm was then instituted. This consisted of the daily ingestion of large amounts of fluid by mouth, the neutral or acid ash diet exactly as outlined by Schemm³ (see diet tables in Appendix of Schemm's article) and the administration of dilute hydrochloric acid. Occasionally ammonium chloride was added to insure an acid residue. Patients were kept in bed at complete rest as before. As in the control period, we avoided using mercurial diuretics or mechanical measures to remove fluid, in order that we might better learn what the regimen alone could accomplish. Mercurial diuretics were sometimes given: (1) at the end of a Schemm period in order to evaluate their effectiveness while the Schemm regimen was being used; or (2), toward the end of the hospital stay to assist in removing residual fluid. The daily intake of fluid varied with the patient's ability to ingest it. An attempt was made to force between 4000 c.c. and 5000 c.c. in 24 hours. Fluids were given only by mouth, and not parenterally.

Evaluation of the clinical status of each patient was made daily. This was based on change in the following symptoms and physical signs: Cyanosis, dyspnea, edema, râles, ascites, liver, pleural effusion. These data were kept on a graphic chart which was compiled each day. These charts are shown in figures 1 to 9 inclusive. Patients were questioned about the palatability of the diet, their ability to take and retain fluids without discomfort, and their reactions to the regimen.

OBSERVATIONS

The data relating to nine patients suffering from congestive heart failure who were treated according to the Schemm plan are presented.

Case 1. D. K. (figure 1): A 23 year old white female had known of the presence of rheumatic heart disease since she was nine. Her first episode of congestive heart failure occurred at 19 at which time she was digitalized. Since that

time she had taken the drug. For two and one-half years before admission she suffered from recurrent ascites and ankle edema for which she received mercupurin two or three times a week. For two weeks before admission she was confined to bed because of increasing dyspnea, orthopnea, ascites and ankle edema which did not respond to mercupurin. On admission the heart was greatly enlarged. Many râles were audible over both lungs. Auricular fibrillation with a ventricular rate of 120

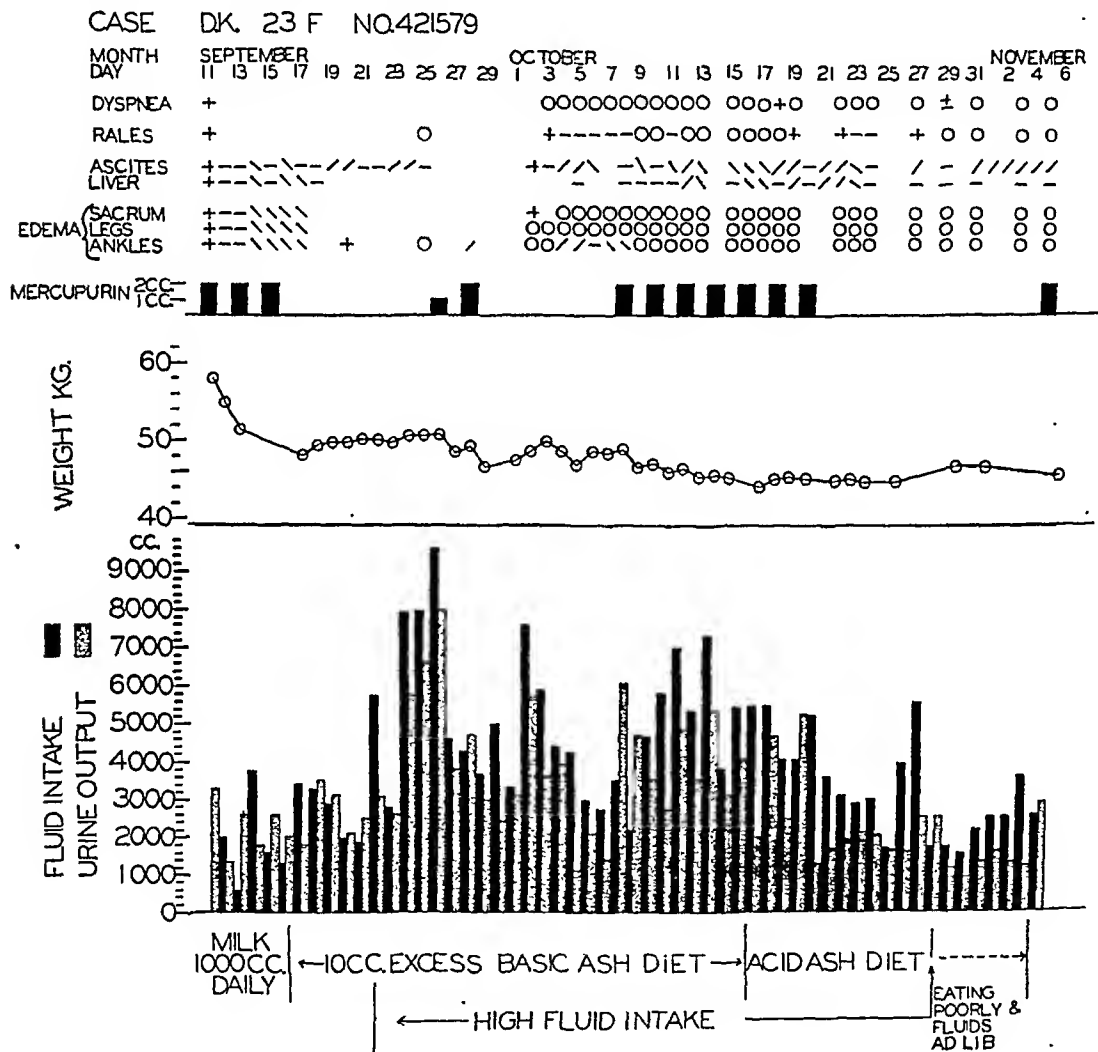


FIG. 1. In this figure are shown data relating to case 1, patient D. K. The clinical status, body weight, and the fluid intake and urine output are recorded for each day. In this figure, as well as in subsequent figures, the presence or absence of signs and symptoms and changes in degree are indicated by the following symbols: + = present, / = increasing, \ = decreasing, - = no change, O = absent.

was present. She had marked ascites; the liver was felt five fingers' breadth below the right costal margin; there was four plus pitting ankle edema. The diagnosis was inactive rheumatic heart disease, cardiac enlargement, mitral stenosis and insufficiency and congestive heart failure.

Because of the rapid ventricular rate she was given supplementary amounts of digitalis. Before she was selected for this study she had been allowed 1000 c.c. of milk daily with no limitation of fluids. She had been given ammonium chloride and had also been given three injections of 2 c.c. mercupurin. Five days on this program

resulted in a weight loss of 6.5 kg. and a marked decrease in edema and ascites. The patient was then placed on a diet low in sodium, equivalent to 10 c.c. of excess basic ash, and ammonium chloride, with vigorous forcing of fluids. As much as 9650 c.c. were taken by mouth in 24 hours without discomfort. Because 2.4 kg. gain in weight occurred after 10 days on this regimen, she was given mercupurin on the eleventh and thirteenth days, which resulted in a weight loss of 3.5 kg. She was then followed for another week on a low sodium, basic ash diet, maintaining a fluid intake between 3000 c.c. and 7600 c.c. daily (average 4500 c.c.). She received no mercupurin. During this time ascites increased gradually and she gained 2.0 kg. in weight. She was then prescribed a course of mercupurin, receiving one injection every other day, which resulted in a weight loss of 4.0 kg. in 13 days.*

At this time the Schemm diet (low sodium, acid ash) was substituted for the basic ash diet, and a high fluid intake and ammonium chloride were continued.† The patient was observed on this regimen without mercupurin for nine days. The fluid intake averaged 3500 c.c. per day, the urine output 1900 c.c. The plasma proteins were 7.9 grams per cent. The venous pressure was equivalent to 190 mm. saline by the direct method. The urine was persistently acid, the specific gravity ranging between 1.005 and 1.027; neither albumin nor casts were present. Edema did not recur, but the ascites remained unchanged or increased slightly, and a weight gain of 1.8 kg. occurred. There was no apparent improvement in the patient's clinical condition. This program was continued, but the observations after nine days were not considered pertinent because bouts of severe abdominal pain believed to be splenic in origin interfered with taking the full diet and the amount of fluid. When it was apparent that no benefit was being obtained by continuing the regimen further, the patient was allowed fluids ad libitum and a low salt diet, and given mercupurin to reduce the ascites. On this regimen ascites decreased slightly and there was a weight loss of 0.9 kg.

Comment: The data in this case illustrate several points: (1) When the Schemm regimen was rigidly applied for nine days without the use of mercupurin, it failed to induce diuresis, and to prevent the slow reaccumulation of ascites. During its use a gain of 1.8 kg. in weight occurred. (2) The urine output consistently failed to approach in amount that of the fluid intake, the average daily urine output being 1900 c.c. and the fluid intake 3500 c.c. (3) Mercupurin was necessary to induce an effective diuresis. (4) Large amounts of fluid were taken without discomfort, and on one occasion 9650 c.c. were taken by mouth in a 24 hour period.

Case 2. L. M. (figure 2): A 34 year old white female, known to have had rheumatic heart disease since childhood, was first digitalized for cardiac decompensation in 1944. Since then she had had three admissions to the New York Hospital because of congestive heart failure, with edema and ascites. Two weeks prior to the present admission a paracentesis was performed to relieve the ascites, but dyspnea, orthopnea, and ankle swelling increased in spite of bed rest at home, three injections of mercupurin weekly, and limitation of salt and fluid. Only 250 to 300 c.c. of urine resulted from each injection of mercupurin. On admission she was very dyspneic and orthopneic. Many moist râles were heard. The heart was greatly enlarged, a presystolic murmur of mitral stenosis at the apex and a systolic murmur of tricuspid insufficiency to the right of the sternum were heard. Auricular fibrillation with a

* The routine employed in administering mercupurin to this patient and to other patients in this study does not concur with the accepted method of one of us (H. J. S.).
† The plans for this study had not been formulated when this first case was admitted to the hospital and the preliminary period was not obtained.

ventricular rate of 86 per minute was present. There was considerable ascites, and the liver edge was felt five fingers' breadth below the costal margin. There was two plus pitting edema of the legs and ankles. The diagnosis was rheumatic heart disease, enlarged heart, mitral stenosis and insufficiency, aortic and tricuspid insufficiency, auricular fibrillation, and cardiac decompensation.

A paracentesis performed on admission because of distress from the ascites and respiratory embarrassment yielded 4100 c.c. of ascitic fluid which resulted in a fall in weight from 54.8 to 51.4 kg.

In the preliminary "control" period of seven days, the patient was at bed rest, and was given a three gram salt diet with 1200 c.c. of fluids daily, and maintenance

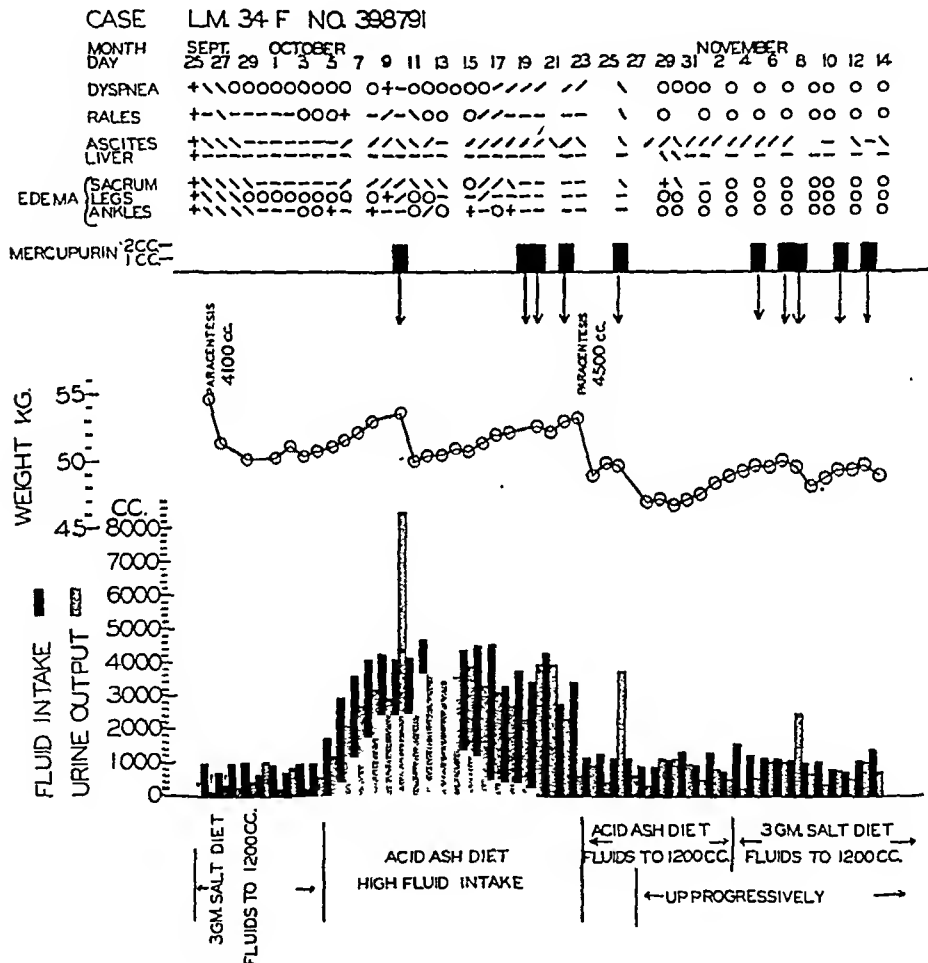


FIG. 2. In this figure are shown data relating to case 2, patient L. M.

amounts of digitalis. The ascites decreased during the first few days following the paracentesis, then remained unchanged. Dyspnea disappeared, and râles were no longer heard in the lungs. Peripheral edema disappeared, but sacral edema persisted. The weight remained stationary. During this period the following data were obtained: Venous pressure 190 mm. saline, circulation time, arm to tongue, 36 seconds (Decholin), vital capacity 1150 c.c., and serum proteins 6.8 grams per cent.

The patient was then given a Scheinm diet, forcing fluids to 5000 c.c. daily, with acidification of the urine by ammonium chloride in doses of 4 to 6 gm. daily. She was kept at bed rest on maintenance amounts of digitalis. This regimen was maintained for 18 days. Mercupurin was not given during the first six days. The average daily

fluid intake was 3800 c.c. The urine remained acid. After six days she had gained 2.5 kg. in weight, and the ascites had increased to the point of discomfort, dyspnea was recurring and râles were again heard in the lungs. Sacral edema was marked. Two c.c. of mercupurin were therefore administered on the sixth day, resulting in an excellent diuresis of 8500 c.c. and a weight loss of 3.6 kg.

The patient was kept for another eight days on the Schemm diet, with a daily fluid intake averaging 4000 c.c. without further mercupurin, and with five drops of dilute hydrochloric acid in each glass of water substituted for the ammonium chloride. The urine remained acid. Again her weight increased, rising from 50.0 to 52.6 kg. Dyspnea returned, ascites increased and sacral edema again became marked. Râles recurred in the lungs, and peripheral edema reappeared.

Two injections of mercupurin were given, without appreciable diuresis or change in weight. Four thousand five hundred c.c. of ascitic fluid were removed by paracentesis. The intake of fluid was reduced at this point, after 18 days on the Schemm regimen with an unfavorable response. In this time the patient's weight had increased from 51.1 to 53.2 kg., a net gain of 2.1 kg., in spite of three injections of mercupurin.

Because of its low sodium content the Schemm diet was continued, but the fluid intake was reduced to 1200 c.c. daily. The patient was now allowed out of bed. One injection of mercupurin was given and the patient became free of edema. After nine days the patient had gained 2.2 kg. She was again given a three gram salt diet, with fluids limited to 1200 c.c. and mercupurin. She lost 0.2 kg. in weight and ascites remained unchanged.

Comment: In this patient an extensive trial of the Schemm regimen was ineffective. With a fluid intake averaging 3800 c.c. daily, the patient gained 2.5 kg. in six days, requiring an injection of mercupurin. After another trial of eight days on an average daily fluid intake of 4000 c.c. it became necessary to resort to a paracentesis because of increase in ascites. The first response to 2 c.c. of mercupurin while on the Schemm program was excellent, resulting in a diuresis of 8500 c.c. in 24 hours. Eight days later, however, while on the same regimen, two injections of mercupurin in the same dosage failed to induce satisfactory diuresis.

Early, the patient was enthusiastic about the Schemm diet, but later she admitted that the three gram salt diet was more palatable, having more variety and a better choice of food.

The patient's long period of hospitalization made it possible to compare the three gram salt diet—1200 c.c. fluid intake regimen on two occasions with the Schemm regimen during a high fluid intake and then with the Schemm diet with 1200 c.c. fluid intake. It was only on a limited fluid intake that she became free of edema and of râles. Ascites recurred sooner during the period of high fluid intake.

Case 3. M. W. (figure 3): A 67 year old white female suffering from rheumatic heart disease was admitted to the hospital on October 27, 1945 for the fourth time because of progressive dyspnea, orthopnea, ascites and edema. On her previous admission in July and August 1945, because of the same symptoms she had been given a low sodium diet equivalent to 10 c.c. excess basic ash and a high fluid intake amounting to 4000 to 5000 c.c. daily. She also received ammonium chloride and mercupurin once weekly during that admission. She responded very well, losing 10.0 kg. in weight, and at the time of discharge she was free of edema and ascites. She

In spite of close adherence to this regimen at home she began to reaccumulate fluid. She was able to take four to five quarts of fluid daily, but she stayed in bed most of the time. During the two weeks before admission she received three injections of mercupurin weekly without benefit.

On admission she was very dyspneic and cyanotic. There were a few moist râles at the lung bases. The heart was markedly enlarged. The typical murmurs of mitral stenosis and insufficiency, aortic stenosis and insufficiency, and tricuspid in-

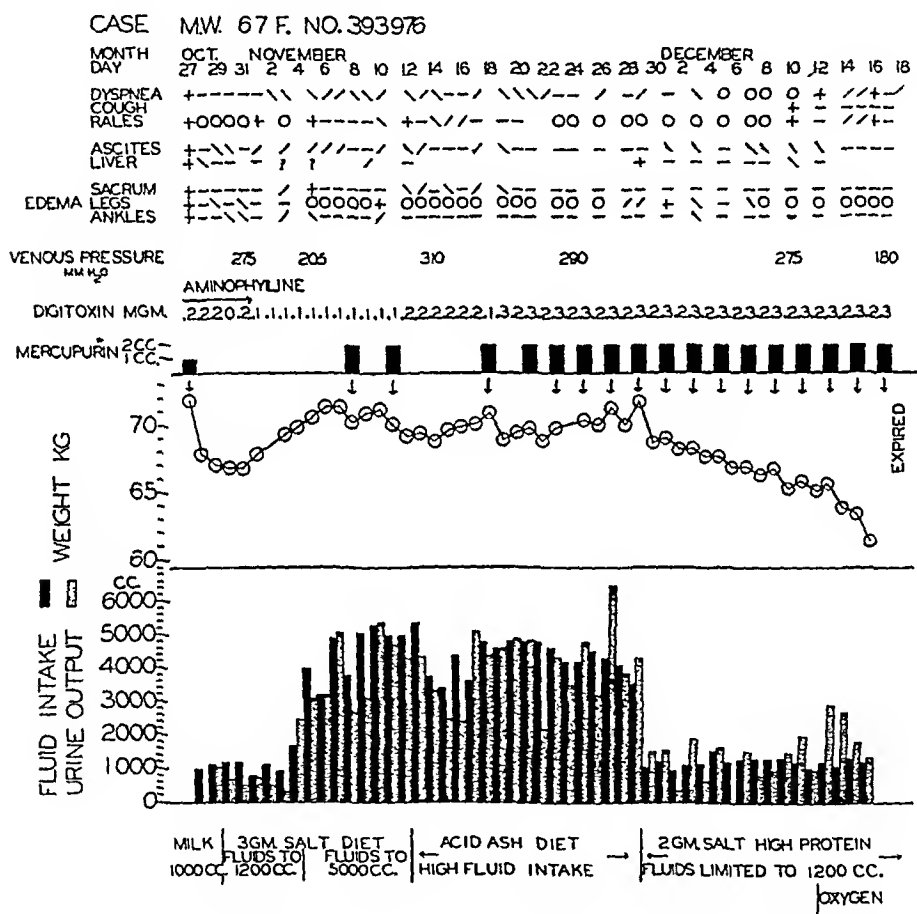


FIG. 3. In this figure are shown data relating to case 3, patient M. W.

sufficiency were present. Auricular fibrillation with a moderately rapid ventricular rate was present. There was considerable ascites. The liver edge was palpable four fingers' breadth below the costal margin. There was two plus sacral and ankle edema. The venous pressure was elevated to 275 mm. of saline, and the arm to tongue circulation time (Decholin) was 19 seconds. Serum proteins were 6.2 grams per cent. The urine showed no albumin or casts, and the specific gravity ranged from 1.003 to 1.022. The diagnosis was rheumatic heart disease, enlarged heart, mitral stenosis and insufficiency, tricuspid insufficiency, auricular fibrillation, and cardiac decompensation.

Upon admission she received 0.2 gm. of aminophylline and 1 c.c. of mercupurin. During a preliminary three day period she was placed on the Karell diet of 1000 c.c. of milk daily, and given aminophylline as a suppository 0.6 gm. daily for three days.

At the end of three days her weight fell from 72.0 to 67.0 kg., a weight loss of 5.0 kg. There was a decrease in edema and ascites.

The "control" period was then instituted and the patient was given a three gram salt diet with limitation of fluids to 1300 c.c. daily. No diuretics were given. After six days her weight had risen from 67.0 to 70.0 kg., a gain of 3.0 kg., and edema and ascites were increasing.

Fluids by mouth were then forced to 5000 c.c. daily, but due to an oversight the Schemm diet was not substituted for the three gram salt diet until eight days later. During this period the patient had begun to gain weight and to experience distress from her ascites. Two injections of mercupurin and aminophylline 0.6 to 0.8 gm. daily (a total of 4.25 gm. in six days) were therefore given with slight loss in weight, but there was very little change in her clinical condition.

The change to the Schemm diet, with forcing of fluids by mouth to 5000 c.c. daily, supplementary acidification with dilute hydrochloric acid or ammonium chloride, inaugurated the trial of the Schemm regimen. During the next six days no mercupurin was given. The daily intake averaged 4400 c.c., the urine output 3500 c.c., the urine remaining acid. The weight increased from 69.6 to 71.0 kg., a gain of 1.4 kg., and the edema, ascites, and râles in the lungs increased slightly. Because it was evident that no improvement was occurring on the Schemm regimen alone it was decided to resort to mercupurin. She was therefore given six injections of mercupurin during the remaining 11 days of the Schemm regimen; during this time she gained weight and edema increased.

Because the Schemm regimen was evidently failing even when supplemented by frequent injections of mercupurin, the patient was now given a two gram salt, high protein diet with restriction of fluids to 1200 c.c. daily. She was kept at complete bed rest, 2 c.c. of mercupurin were given every other day. She also received 4 grams of ammonium chloride daily. During the 17 days that she was on this program her weight fell from 68.8 to 61.4 kg., a net weight loss of 7.4 kg. Ankle edema decreased slightly, and although she still had sacral edema, the ascites had now nearly disappeared. The patient appeared to be doing well at this point, when she suddenly developed a cough and fever, and rapidly the signs of bronchopneumonia appeared. She died six days later. At autopsy very little fluid was present in the pleural and peritoneal cavities. Her weight just before death was 61.4 kg.

Comment: The advanced stage of this patient's heart disease was confirmed at autopsy. The heart was greatly enlarged, and there was extensive involvement of the mitral, aortic and tricuspid valves. The presence of tricuspid insufficiency was suspected some time before death because of the characteristic murmur in the tricuspid area and the pulsating liver, and this diagnosis was confirmed at autopsy. Coarsely nodular cirrhosis of the liver with congestion was found at autopsy, as well as severe chronic passive congestion of the kidneys and other viscera. The venous pressure was at all times markedly elevated, and was usually between 275 and 310 mm. saline. On the Schemm regimen the average daily fluid intake was 4400 c.c., while the average daily urine output was only 3500 c.c. without mercupurin.

After six days on the Schemm regimen without mercupurin, the patient gained 1.4 kg. in weight and after 11 more days on the regimen during which time she received six injections of mercupurin, she gained another 0.9 kg. There was no improvement in the patient's condition. Mercupurin while on the acid ash diet and high fluid intake was ineffective, but was effective after

the patient was placed on a two gram salt, high protein diet with restriction of fluids. The patient did not care for the Schemm diet, remarking on the limited variety of foods, and the exclusion of the more palatable foods. She frequently had difficulty in drinking more than 4000 c.c. of fluid a day, complaining of a feeling of fullness, and inability to eat all the food in the diet.

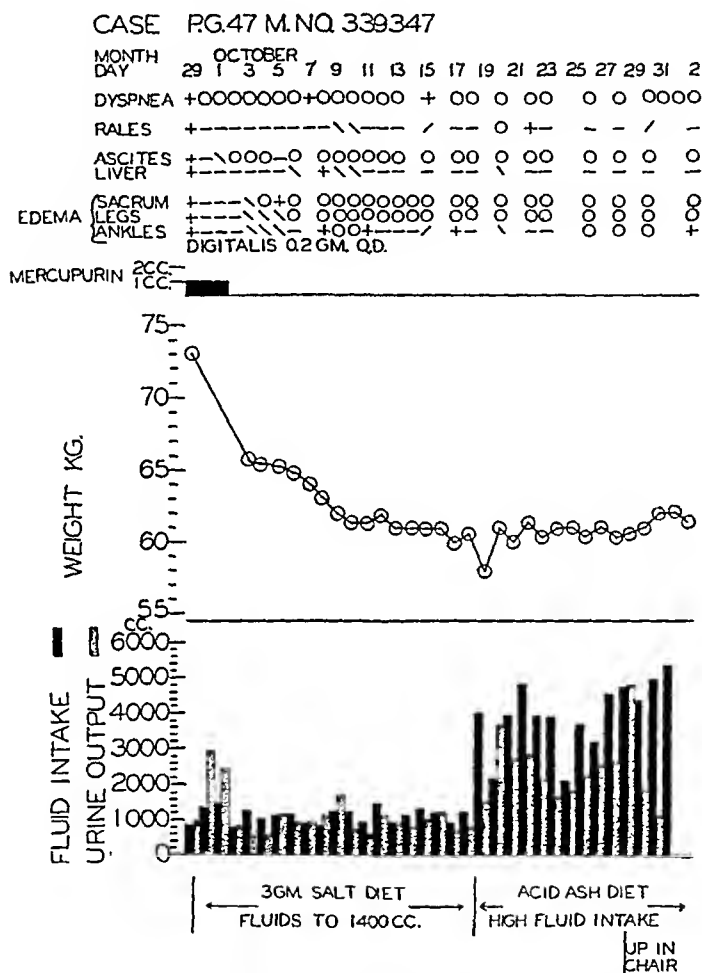


FIG. 4. In this figure are shown data relating to case 4, patient P. G.

Case 4. P. G. (figure 4): A 47 year old white male was admitted to the hospital on September 29, 1945. The patient had been in good health until the first hospital admission in September 1942 at the age of 44 because of progressive signs and symptoms of heart failure of several months' duration. He had dyspnea, orthopnea, fluid in the right pleural cavity, an enlarged heart, an enlarged liver without ascites, and marked edema of the legs and ankles. An electrocardiogram showed bundle branch block. On bed rest, digitalization, restriction of salt and fluid, and diuretics, he improved rapidly and was discharged with a diagnosis of arteriosclerotic heart disease and cardiac failure. One year later he was readmitted because the same signs and symptoms of heart failure had recurred after he had stopped taking digitalis. He was again digitalized; he improved rapidly when given the same therapy as on the first admission and was discharged. In the interval between admissions he had been followed in the cardiac clinic on a regimen of maintenance amounts of digitalis, ammonium chloride, and occasional injections of mercupurin. The third admission in

December 1944 for heart failure followed an upper respiratory infection two weeks earlier. After a month at bed rest on a three gram salt diet and fluid restriction to 1200 c.c. daily, and mercupurin injections three times weekly, he was discharged improved.

The patient was well, attending the cardiac clinic at two week intervals until August 1945, one month before his present admission. He omitted his weekly injections of mercupurin while away on a month's vacation. His weight gradually increased, and dysnea, orthopnea and edema recurred. He had limited fluids to six glasses daily, but no effort was made to restrict the salt intake.

On admission he exhibited râles in the lungs, fluid at the right base, an enlarged liver, and scrotal, sacral and ankle edema. There was no ascites. The venous pressure was 78 mm. of saline, arm to tongue circulation time (Decholin) 27 seconds. Serum proteins were 8.0 grams per cent. The diagnosis was heart disease of unknown etiology, enlarged heart, normal sinus rhythm, and cardiac decompensation.

The patient was put at complete bed rest and given a three gram salt diet, fluids to 1500 c.c. daily, and maintenance amounts of digitoxin. He was given 2 c.c. of mercupurin for three doses on the first three days. Because of the possibility of vitamin deficiency he was given large amounts of supplementary vitamins, including nicotinic acid and thiamine hydrochloride. He was kept on this program for 18 days without further use of mercupurin. In this time he lost 13.0 kg. in weight, 8.0 kg. of which apparently resulted from the administration of mercupurin. Râles persisted in the lungs and there was little change in the size of the liver, but peripheral edema became much less.

When the weight had stabilized, the patient was given the Schemm regimen and fluids were forced to 4500 c.c. daily. At first the fluid intake fell below this figure, but he was soon able to take the prescribed amount daily without difficulty. The acid ash diet was supplemented with five drops of dilute hydrochloric acid in each glass of water. Bed rest was continued, with commode privileges allowed. He received no mercupurin. The urine remained acid during the entire period. There was no evidence of impaired renal function. The Schemm regimen was maintained for 15 days. The average daily fluid intake was 4000 c.c., urine output 2200 c.c. At times he complained that the large quantity of water interfered with eating his full diet. He seemed to prefer the Schemm diet to the three gram salt diet without offering any reason for the preference. A weight gain of 0.8 kg. occurred on the Schemm regimen. Râles did not increase and a roentgenogram of the lungs at the end of this period showed minimal clearing of the pleural effusion and pulmonary congestion. The size of the liver may have decreased slightly, but slight ankle edema returned later in this period. During the last week of hospital stay, he was allowed up progressively. The Schemm regimen was continued until discharge from the hospital.

Comment: This patient suffering from arteriosclerotic heart disease with congestive failure exhibited by pulmonary congestion and peripheral edema was observed on the Schemm regimen without mercupurin for 15 days. Although not an ideal case for evaluating the Schemm regimen because of the disappearance of nearly all the edema during the "control" period, it was decided to test the Schemm regimen in the presence of a moderate degree of failure and also to observe whether diuresis could be effected by the regimen, or whether fluid reaccumulated if large quantities of fluid were given without mercurial diuretics. The average daily fluid intake was 4000 c.c.; even in the absence of demonstrable renal impairment, the urine output averaged only 2200 c.c. After two weeks on the regimen a weight gain of 0.8 kg. had

occurred, no diuresis had been evoked, and there was evidence of increasing ankle edema and fluid reaccumulation.

Case 5. M. R. (figure 5): A 56 year old white female was well until two years before admission when she experienced sudden severe pain in the left chest. She was told she had heart trouble and was given digitalis. Several similar attacks occurred in 1943 and 1944. Three months before admission she had another attack of severe stabbing pain in the left chest, after which she experienced progressive dyspnea,

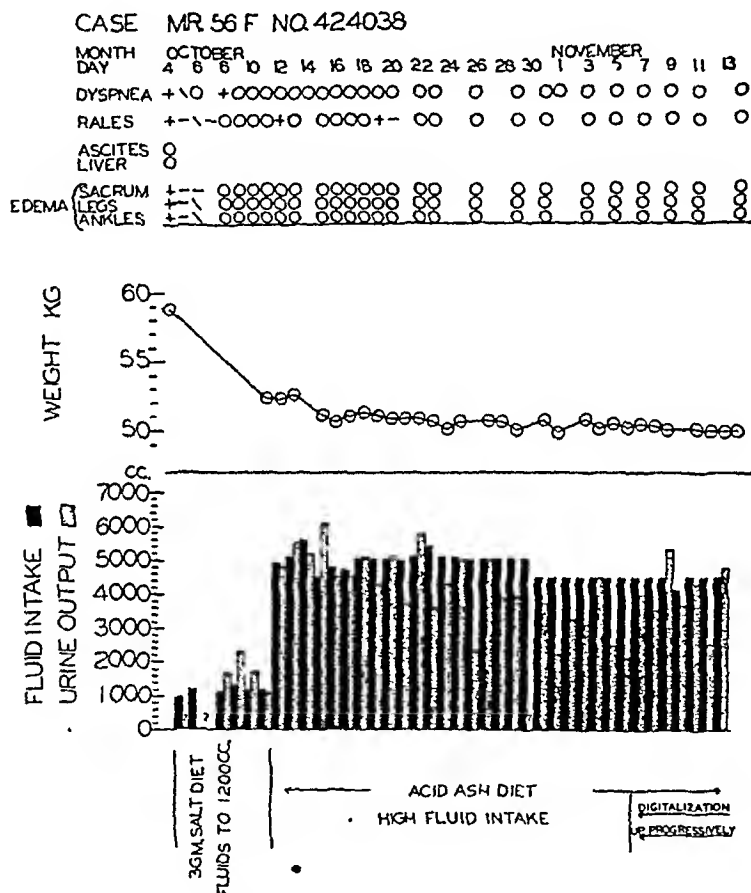


FIG. 5. In this figure are shown data relating to case 5, patient M. R.

orthopnea and ankle edema. At the time of admission the patient was fairly active, and was not taking digitalis, nor restricting salt and fluid intake.

On admission she exhibited dyspnea, orthopnea and râles at both lung bases as evidence of cardiac failure. There was no ascites; the liver was palpable three fingers' breadth below the costal margin and was tender. There was two plus sacral edema and one plus ankle edema. The venous pressure was 125 mm. saline, and the arm to tongue circulation time (Decholin) was 27 seconds. The serum proteins were 6.7 grams per cent. The urine was clear, without albumin or casts. The specific gravity ranged between 1.005 to 1.012. The diagnosis was arteriosclerotic heart disease, possible coronary artery disease, normal sinus rhythm, cardiac decompensation.

The preliminary "control" period was instituted with the patient at complete bed rest, on a three gram salt diet, and fluids restricted to 1200 c.c. daily. She was not given digitalis or diuretics. This program was maintained for seven days, during

which time there occurred a fall in weight from 58.8 to 52.4 kg., a net loss of 6.4 kg. The fluid intake averaged 1100 c.c. The râles and the edema disappeared, but the size of the liver remained unchanged.

The Schemm regimen was then instituted; the daily fluid intake amounted to 5000 c.c. of fluid with five drops of dilute hydrochloric acid in each glass of water. She was kept at bed rest and received no mercupurin. She said that she preferred the Schemm diet to the three gram salt diet, although she gave no reason for this choice. She appeared to have no difficulty taking 5000 c.c. of fluid, although she preferred to take only 4500 c.c., the amount to which she was later changed, because the larger amount was "tiresome." The Schemm regimen was maintained for 26 days. The fluid intake averaged 5000 c.c., and the urine output 4200 c.c. daily. Acidity of the urine was maintained. The weight fell from 52.4 to 50.3 kg., a weight loss of 2.1 kg. There was no change in her clinical status, and no evidence of reaccumulation of fluid. There was no change in levels of venous pressure, circulation time, vital capacity, serum proteins, chlorides, blood count and hematocrit. Progressive changes in serial electrocardiograms during this time suggested that coronary occlusion had occurred before admission.

Following the trial period the Schemm diet was continued, fluids were reduced to 4500 c.c. daily, and the patient was digitalized and allowed out of bed progressively. This resulted in a weight loss of 0.3 kg. in seven days. The patient was discharged on maintenance amounts of digitalis.

Comment: This patient placed on the Schemm regimen for 26 days, lost 2.1 kg. in weight. The average fluid intake was 5000 c.c. daily, and the urine output 4200 c.c. In short, in this instance on the Schemm regimen the patient lost weight and was maintained free of edema and of fluid accumulation without the use of mercurial diuretics. The data show that the use of this regimen in this patient whose urine output was commensurate with the fluid intake, did not lead to accumulation of fluids even without the use of mercupurin.

Case 6. G. M. (figure 6): This 34 year old white male, who had a history of two attacks of rheumatic polyarthritis at 12 and 23 years of age, first developed dyspnea on exertion one and a half years before admission. He was digitalized at that time, and continued to take 0.2 gram daily. Seven months before admission he suffered from a severe cold, associated with chilliness and cold sweats; two months before admission he developed dyspnea again, followed by progressive orthopnea and ankle edema. He received five injections of mercupurin during the month before admission, but none for seven days before admission. He had been very active up to admission. He denied the use of salt on his food, but had not been restricting fluids.

On admission the patient exhibited signs of moderately advanced cardiac failure. He was dyspneic and cyanotic, and moist râles were heard in both lungs. The heart was markedly enlarged. Its rhythm was regular with occasional premature contractions. A presystolic murmur of mitral stenosis and a systolic murmur of mitral insufficiency were heard at the apex. There was a pulmonic diastolic murmur as well. Moderate ascites was present. The liver edge was palpable five fingers' breadth below the costal margin and was tender. There was two plus sacral and four plus ankle edema. The diagnosis was rheumatic heart disease, enlarged heart, mitral stenosis and insufficiency, normal sinus rhythm, cardiac decompensation.

The possibility of subacute bacterial endocarditis was entertained, but repeated blood cultures were negative. Intravenous pyelograms showed poorly functioning kidneys, and on one occasion a culture of the urine revealed *B. lactis aerogenes*. The

red blood cell count was 6.0 million and the hemoglobin estimation was 18 grams. The venous pressure was 120 mm. saline. Serum proteins were 6.2 grams per cent.

During the preliminary "control" period the patient was put at bed rest, given a three gram salt diet and allowed fluids to 2000 c.c. for the first five days because of excessive sweating; the fluid intake was then reduced to 1500 c.c. daily. Digitoxin 0.2 mg. was given daily. Other diuretics were not used. The patient was maintained on this program for 12 days. The weight fell from 98.0 to 96.0 kg. Dyspnea was much relieved although a few râles were still heard at the lung bases. Ankle edema

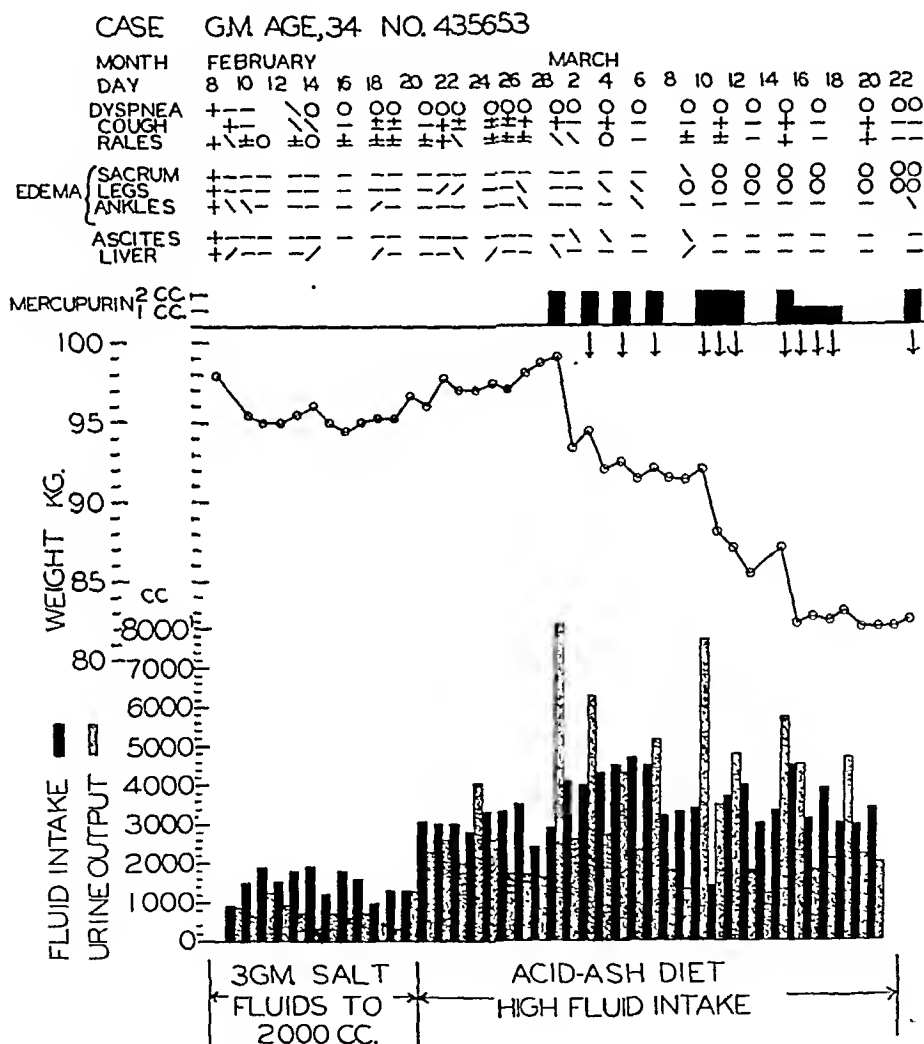


FIG. 6. In this figure are shown data relating to case 6, patient G. M.

decreased from four to two plus. The ascites remained unchanged, but the size of the liver increased.

The Schemm regimen was then instituted, the patient still remaining at bed rest; this included the Schemm diet, and high fluid intake, acidified with five to eight drops of dilute hydrochloric acid in each glass of water. No mercurial diuretics were given. This regimen was continued for eight days. The average oral daily fluid intake was 3000 c.c., the urine output 2300 c.c. The urine was at first acid in reaction, later becoming neutral, and once slightly alkaline at a time when cultures revealed *B. lactis aerogenes*. The weight increased from 96.0 to 99.0 kg., a gain of 3.0 kg. Slight cyanosis appeared. Edema and ascites remained unchanged. The liver edge was

now felt six fingers' breadth below the costal margin. Edema of the anterior abdominal wall was frequently distressing.

The persistent weight gain and apparent failure of the regimen led to the decision to test the effect of mercupurin while the Schemm regimen was maintained and increasing the dilute hydrochloric acid from eight to ten drops per glass. The first injection of 2 c.c. of mercupurin produced a marked diuresis of 8000 c.c. in 24 hours, resulting in a weight loss of 5.7 kg. Two c.c. of mercupurin were given every other day for a period of 23 days during which the weight fell from 99.0 to 82.0 kg., a loss of 17.0 kg. The average daily fluid intake during this period was 3600 c.c., and the urine output was 3000 c.c. The most effective diuresis occurred when the urine was acid. Edema disappeared except from the ankles and ascites disappeared, râles in the lungs cleared, but the size of the liver remained unchanged. Fever, recurrent hemoptysis and a persistent urinary tract infection were complications requiring special therapy. Measures which would not introduce factors tending to invalidate the results of the regimen were employed.

During the last 24 days of hospital stay, the patient was given a 2000 calorie diet containing three grams of salt, with fluids to 2000 c.c. daily, and 8.0 gm. ammonium chloride. He received 2 c.c. mercupurin every other day. He was allowed up progressively. The weight had fallen from 79.6 to 74.4 kg. at the time of discharge, a loss of 5.2 kg.

Comment: The Schemm regimen was used in this case for a period of eight days. The patient coöperated well, taking an average of 3000 c.c. of fluids daily; he complained frequently of the inadequacy in amount and variety of the diet. The urine output never approached the fluid intake, averaging only 2300 c.c. daily. The Schemm regimen without the use of mercupurin was unsuccessful in the alleviation of heart failure as the patient gained 3.0 kg. in weight, and showed increase in edema, size of the liver or amount of ascites.

Excellent diuresis occurred, however, when mercupurin was used in conjunction with the Schemm regimen. The initial 2 c.c. injection evoked a diuresis of 8000 c.c. After 11 injections in 23 days, the patient was relieved of fluid accumulations, losing 17 kg., while on the low sodium diet and a fluid intake averaging 3600 c.c. daily. The patient also lost weight on a three gram salt diet with fluids around 2000 c.c. daily, together with ammonium chloride and mercupurin.

Case 7. A. H. (figure 7): A 63 year old white male was admitted to hospital on December 26, 1945 for the first time. He had experienced swelling of the ankles for six months, and dyspnea and orthopnea for four months. Digitalization was begun four days before admission and 1.0 c.c. of mercupurin given. On admission, dyspnea, orthopnea and cyanosis were present. Moist râles were heard in the lower half of both lung fields. The heart was enlarged to the anterior axillary line. The blood pressure was 150 mm. Hg systolic and 94 mm. Hg diastolic. There was no ascites. The liver edge was felt four fingers' breadth below the costal margin. There was four plus pitting edema of the legs and ankles. The diagnosis was arteriosclerotic heart disease with cardiac enlargement, cardiac decompensation, and normal rhythm.

A roentgenogram of the chest showed a deformed thorax with kyphoscoliosis, and increased vascular markings with pulmonary fibrosis and emphysema. The red blood cell count was 6.0 million, the hemoglobin 18.0 gm., the hematocrit 68 per cent. The venous pressure was 105 mm. saline and the circulation time (calcium gluconate)

was 18 seconds. The serum proteins measured 6.0 grams per cent. The urine concentration reached 1,020. Albumin and casts were not detected.

On admission the patient was given mercupurin, 2 c.c. and aminophylline, 0.5 gram before it was decided to use the Schemm regimen. These measures resulted in a fall in weight from 57.2 to 53.0 kg. A "control" period was then instituted, in which the patient was at complete bed rest, given a three gram salt diet with daily

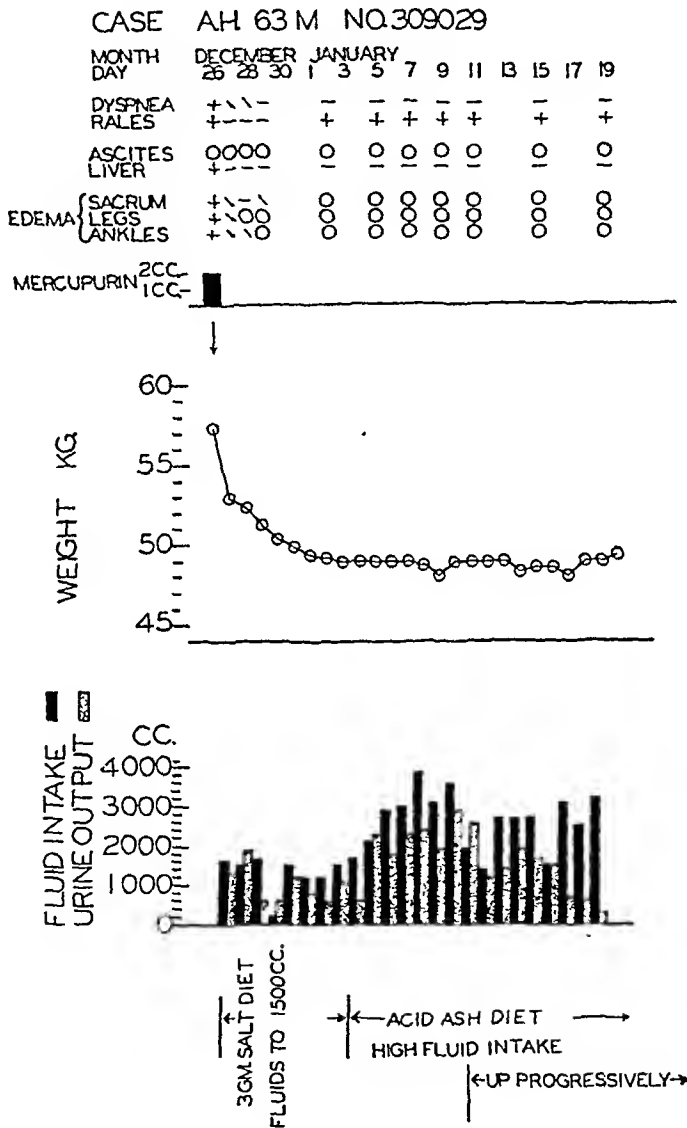


FIG. 7. In this figure are shown data relating to case 7, patient A. H.

fluid intake limited to 1500 c.c. Maintenance amounts of digitalis were continued. This program was continued without other diuretics for eight days. The weight fell from 53.0 to 49.0 kg., a loss of 4.0 kg. Peripheral edema disappeared. Râles persisted in the lungs and the size of the liver did not change.

After several days, when the weight had stabilized at 49.0 kg., and there was no further apparent change in the patient's condition, the Schemm regimen was instituted. An attempt was made to force fluids to 4000 c.c. daily. The patient was given ammonium chloride, 4.0 grams daily, instead of dilute hydrochloric acid, but received no other diuretics. Maintenance amounts of digitalis were continued. The average

daily fluid intake was 3000 c.c., the urine output 2300 c.c. The urine remained acid at pH 4.5. During the eight day trial of the Schemm regimen without mercupurin and on strict bed rest, there was no change in the weight or in the patient's clinical status. Râles in the lungs persisted. There was no change in the size of the liver. There was no evidence that fluid was reaccumulating. Decrease in the heart size was observed in the roentgenogram of the chest taken at the end of this period, and vascular markings in the lung fields had become less prominent.

The Schemm regimen was continued, the patient, however, now being allowed up progressively. No diuretics were given. After nine days there was a slight weight gain of 0.4 kg., but no significant change in the clinical status occurred.

Comment: This 63 year old patient exhibiting evidence of arteriosclerotic heart disease, pulmonary fibrosis and emphysema, who suffered from cardiac failure was given a trial of the Schemm regimen without mercupurin for eight days. Although all peripheral edema had cleared during the control period, there was still pulmonary congestion and enlargement of the liver. When on strict bed rest for eight days on the Schemm regimen with oral fluid intake of 3000 c.c. daily the patient failed to exhibit significant change in weight and diuresis did not occur. A subsequent period of nine days on the Schemm regimen with the patient permitted ambulatory privileges did not result in increase in signs of failure.

Case 8. F. S. (figure 8): A 56 year old white female who had known of her hypertension for many years was admitted to the hospital giving a history of progressive dyspnea, orthopnea, and swelling of the ankles of three months' duration. Recurrent episodes of dyspnea and swelling of the ankles had occurred for at least four years. During the six weeks before admission she had been given digitoxin 0.2 mg., and ammonium chloride, 4.0 gm. daily, and mercupurin once a week without apparent relief. She had continued active without limiting salt and fluid intake.

She was obese, orthopneic, and dyspneic on the slightest exertion. Advanced hypertensive retinopathy was present. There was decreased resonance in the lower half of the right lung field. Many fine crepitant râles were heard in this area. The heart was greatly enlarged. Auricular fibrillation was present, with a ventricular rate of 84 per min. There was no ascites. The liver was felt three fingers' breadth below the costal margin. One plus sacral edema and two plus ankle edema were present.

A roentgenogram of the chest revealed cardiac enlargement, most marked in the region of the left ventricle, and an area of atelectasis or consolidation in the middle lobe of the right lung. The electrocardiogram showed auricular fibrillation with a ventricular rate of 90. The venous pressure was 60 mm. of saline. Arm to tongue circulation time (Decholin) was 23 seconds. Serum proteins were 7.1 gm. per cent. The urine was free of casts and albumin. The urine concentration was 1.023. The diagnosis was hypertensive and arteriosclerotic cardiovascular disease, enlarged heart, cardiac decompensation, and auricular fibrillation.

The "control" period was instituted for five days until the patient's weight stabilized: This consisted of complete bed rest, three gram salt diet, 1200 c.c. fluids and maintenance amounts of digitoxin. Mercupurin was not given. The average daily fluid intake was 850 c.c., the urine output 740 c.c. She lost 1.4 kg. in weight during this period, but continued to have orthopnea and dyspnea on the slightest exertion. There was no change in the signs in the right lung, or in the size of the liver, but ankle edema decreased. One injection of aminophylline, 0.5 gm. intravenously was required for relief of dyspnea. During the last two days of the control period there was no appreciable change in weight.

The Schemm regimen was then started: The Schemm diet, forcing of fluids and five drops of dilute hydrochloric acid added to each glass of water. She received no diuretics. This plan was continued for seven days. The average daily fluid intake was 3800 c.c., the urine output was 2800 c.c. All urine specimens were acid. There was no change in weight or in the patient's clinical status. Peripheral edema was

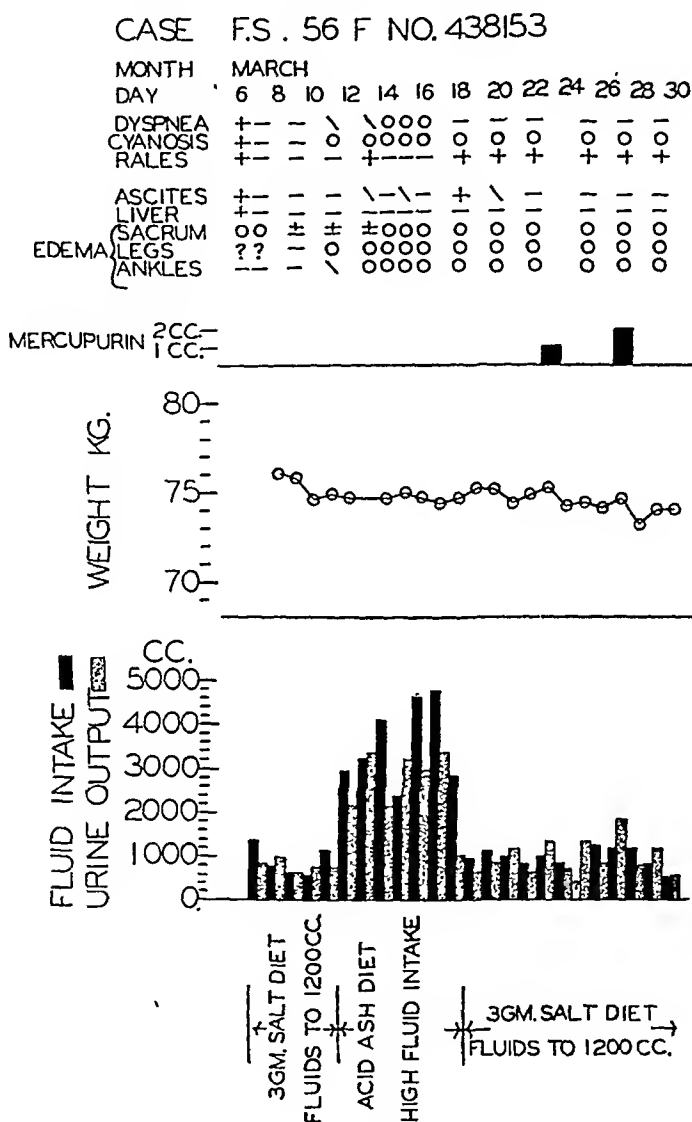


FIG. 8. In this figure are shown data relating to case 8, patient F. S.

no longer apparent, but the liver did not change in size. A second roentgen-ray of the chest showed slight decrease in pulmonary congestion.

Because of the failure of the Schemm regimen to induce diuresis the use of the three gram salt diet and restriction of fluids to 1200 c.c. was instituted. There was no significant change in weight after five days. Mercupurin was then given, resulting in moderate diuresis. The patient was kept on this program until discharge. There was no apparent improvement in clinical state, and further change in the roentgen-ray shadows in right middle lobe was not observed.

Comment: This patient with hypertensive heart disease, suffering from congestive heart failure was given a trial on the Schemm regimen without

mercurial diuretics for seven days. The patient took an average of 3800 c.c. of fluids daily, but frequently complained that it was difficult to drink this amount. She did not like the Schemm diet, preferring the three gram salt diet, and she commented on the poor choice of food. Her urine output never approached her intake. The Schemm regimen in this instance failed to induce diuresis, and resulted in no significant change in weight and no improvement in the patient's clinical status.

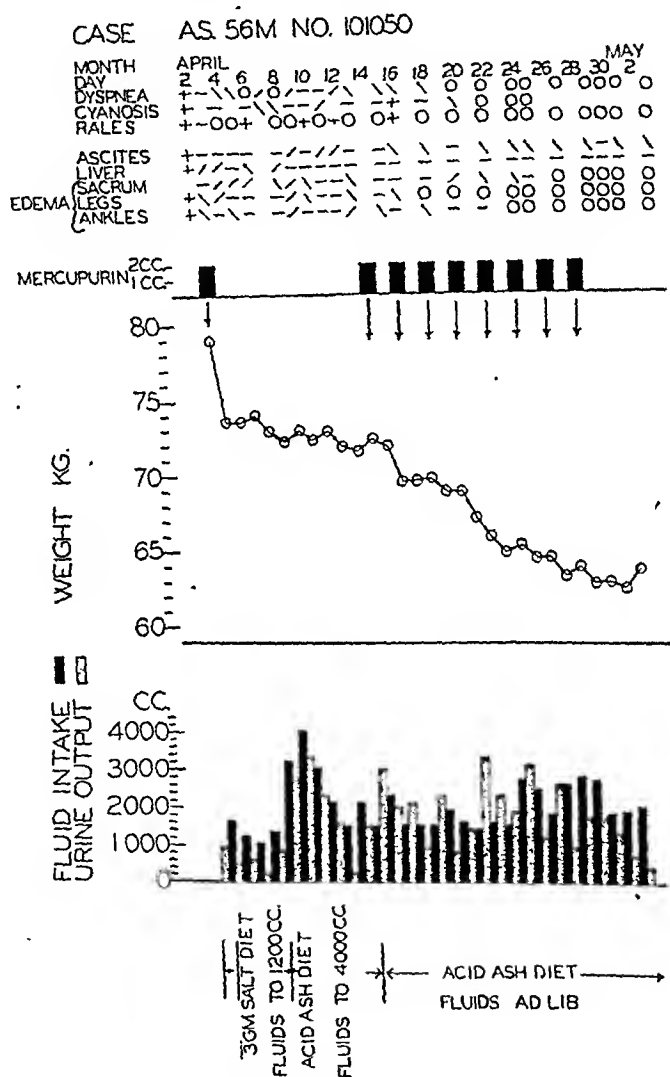


FIG. 9. In this figure are shown data relating to case 9, patient A. S.

Case 9. A. S. (figure 9): A 56 year old white male with known rheumatic heart disease since the age of seven first developed symptoms of heart failure 10 years before admission. Dyspnea, orthopnea and ankle edema occurred five years ago, and one year ago abdominal swelling was first observed. He was digitalized seven months before admission and had been given 1 c.c. of mercupurin weekly during the past four months. No attempt was made to limit salt or fluid intake and the patient had been ambulatory, although not working.

The patient was admitted to hospital on May 2, 1946. He was very dyspneic and cyanotic with marked distention of the neck veins. Moist crackling râles were

heard throughout both lung fields. The heart was greatly enlarged and its rhythm was totally irregular. A harsh blowing apical systolic murmur was transmitted to the axilla, and a soft diastolic murmur was heard at the apex. Ascites was present. The liver was palpable four fingers' breadth below the costal margin. There was three plus pitting sacral and ankle edema. A roentgenogram of the chest showed generalized cardiac enlargement and pulmonary congestion. The venous pressure measured 275 mm. of saline. The serum protein measured 6.6 grams per cent. The diagnosis was rheumatic heart disease, mitral stenosis and insufficiency, enlarged heart, cardiac decompensation, and auricular fibrillation.

On the day of admission the patient was given 2 c.c. of mercupurin to relieve the extreme dyspnea. The weight fell from 79.0 to 73.6 kg. in 24 hours, and the edema in the legs and ankles decreased. The patient remained at complete bed rest, on a three gram salt diet, with fluids limited to 1200 c.c. daily, but additional mercupurin was not given. After four days on this program there was a weight loss of 1.2 kg. Edema, ascites, and size of the liver remained essentially unchanged. The dyspnea was less severe and there was decrease in the signs of pulmonary congestion.

At this point the Schemm regimen was instituted consisting of bed rest, the Schemm diet, and an attempt made to force fluids by mouth to 4000 c.c. daily. Five drops of dilute hydrochloric acid were added to each glass of water, but mercurial diuretics were not given. This regimen was maintained for six days. During the first three days the fluid intake was satisfactory, averaging 3400 c.c. daily and the urine output averaging 2800 c.c. During the second half of this period abdominal fullness and distress resulted in a decrease in the daily fluid intake to an average of 2800 c.c. The average daily urine output fell to 1500 c.c.; the urine specimens remained acid in reaction. There was no change in weight and improvement was not evident. Râles persisted in the lungs; the sacral, leg, and ankle edema, and the size of the liver remained unchanged. The ascites may have increased slightly. During the last two days of the Schemm regimen upper abdominal pain and distention became severe, particularly after eating or taking fluids. The liver became extremely tender. Increasing dyspnea and cyanosis were observed and more râles were heard at the left lung base, posteriorly.

Because of the increase in the patient's signs and symptoms of heart failure the use of mercupurin was indicated. Eight 2 c.c. injections were given every other day for the next 15 days. The Schemm program was continued and the patient was encouraged to take fluids freely, which were not pushed beyond the limit of comfort or tolerance. The average daily fluid intake was 1900 c.c., the average urine output rising to 2000 c.c. A weight loss of 9.4 kg. occurred. Râles in the lungs and edema of the sacrum and extremities disappeared, and the ascites diminished markedly. The size of the liver was unchanged.

The Schemm regimen without mercupurin was resumed during the last four days of hospital stay, in an effort to observe its effect after mercurial diuresis had cleared the edema. A weight gain of 0.8 kg. occurred in this period.

The patient was discharged on the Schemm regimen with instructions to take four grams of ammonium chloride daily, with a liberal quantity of water. He was allowed semi-ambulatory privileges at home. He was seen two weeks later in the cardiac out-patient clinic where it was found that the weight had increased 5.8 kg. He stated that he had adhered rigidly to the prescribed diet, and had received no mercupurin at home. The lungs were clear on auscultation, but ankle edema had recurred and there was a slight increase in the ascites.

Comment: The effect of the Schemm regimen without diuretics was observed in this patient suffering from advanced rheumatic heart disease with moderately severe heart failure. The regimen had to be supplemented with mercupurin after six days because of abdominal distress and accumulating

ascites. The fluid intake during the first three days averaged 3400 c.c., this figure falling to an average of 2800 c.c. with the occurrence of abdominal pain. The urine output did not approach the intake until mercupurin was administered. After an adequate period of diuresis, the effect of the Schemm regimen without mercupurin was again tried, but after four days fluid reaccumulated. Follow-up examination two weeks after discharge from the hospital on the Schemm regimen, revealed considerable weight gain and the reappearance of peripheral edema. In this case two trials of the Schemm regimen without mercupurin were made, one while the patient was still edematous, and the other after an effective diuresis had been obtained, and in both instances there was evidence that fluid reaccumulated on the regimen.

DISCUSSION

In our experience the Schemm regimen has not been successful as a diuretic procedure in the treatment of heart failure. When heart failure was present it did not induce diuresis beyond the amount of the fluid intake, so that there was no loss in the accumulation of fluid. There was increase in urine output with the increase in fluid intake, but only rarely did the output exceed the intake so that there was a net addition of fluid to the body. In our analysis of the charts reproduced in the Schemm papers,^{3, 4, 5} we are unable to observe diuresis from this regimen; the only occasions when the urine output rose above the fluid intake and the patients lost weight were when mercupurin was given. In the controlled observations as we made them it was readily apparent that the regimen was not effective in the mobilization of fluid. Our series is small, but we are of the opinion that a few patients with adequate control periods yield more convincing data than those without control periods. It would be unusual, in our series with the cross section of heart failure we observed, not to have come upon cases in which the regimen was effective, if it is as beneficial as it is claimed to be. The observations which Bridges, Wheeler, and White⁶ and Wheeler, Bridges and White⁷ reported, with the charts which were published are also unconvincing that this regimen is effective in the treatment of heart failure.

The results of Leevy, Strazza and Jaffin⁸ are not reported in such a manner that it is possible to analyze the effects of the procedures used. Data are not presented which allow study of the effectiveness of restricted fluids, fluids ad libitum and forced fluids, in the treatment of heart failure. There are no control periods, so that it is not possible to ascertain whether the patients on the fluid schedules might not have done as well or better on the restricted fluid and salt regimen.

Grollman⁹ showed that drinking water increased the cardiac output as much as 26 per cent in some subjects and around 10 per cent in most subjects. If fluids are forced this implies that during a large part of the day there is an increased load on the heart in trying to maintain an increased output; it is recalled that in the presence of heart failure the cardiac output in most instances is seriously compromised (Stewart, et al.^{10, 11}).

Our observations were conducted on nine patients suffering from congestive heart failure. We selected patients who had visible or demonstrable accumulations of fluid, such as peripheral edema, ascites, hydrothorax or pulmonary congestion in order to gauge the clinical response more accurately. Since diet and activity were carefully controlled, we considered changes in weight and urine output a reliable measure of the response to the control period and the period of the Schemm regimen.

In 10 trials of the Schemm regimen without the addition of diuretics in which nine of the patients concerned were suffering from congestive heart failure, there was not a single instance of a definite clinical improvement of symptoms or of disappearance of edema. The regimen was maintained for periods of from four to 26 days; in most of the patients it was continued for about one week. In all cases an apparently adequate oral fluid intake was obtained. Fluid intakes averaged from 3000 c.c. to 5000 c.c. daily.

Six trials of the Schemm regimen in six patients (Cases no. 1, 2, 3, 4, 6, 9) resulted in a weight gain ranging from 0.8 kg. to 3.0 kg. In only one patient was there a loss of weight; in this instance 2.1 kg. were lost during a 26 day period in which the patient's daily fluid intake averaged 5000 c.c. The clinical response in this case was difficult to estimate, since fluid accumulations were minimal at the beginning of the trial on the Schemm regimen; there was, however, no evidence that edema was recurring during the period of the high fluid intake. In three cases (Cases no. 7, 8, 9) no weight changes occurred, but on the other hand, no evidence of clinical improvement could be observed.

It should be stressed that these observations were made without the use of mercurial diuretics. It is not possible to evaluate a response of the patient to a high fluid intake when mercupurin or other diuretics are given frequently during the course of the regimen. It must be pointed out that in almost all of the charts Schemm used as illustrations of the beneficial effect of the regimen, mercupurin was given at frequent intervals together with the high fluid regimen under study. In analyzing the data relating to his cases we observed that the improvement in the edema appeared to be largely due to the mercupurin, and it was impossible to divorce the effects of the diuretic from the possible beneficial results of the high fluid intake. We have, therefore, withheld mercurial diuretics during the trial period on the Schemm regimen, except in the rare instances when its use was urgently required or after it was apparent that the regimen was ineffective without its use.

We have also considered it essential, in order to arrive at a proper evaluation of each patient's responses on the regimen, to observe the patient during a preliminary period and to allow the patient's status with respect to weight, and clinical signs of heart failure to become stabilized or increase before testing the effect of the Schemm regimen. Our "control" period consisted of a standard two to three gram salt diet, restriction of fluids to a fixed amount, and bed rest. No diuretics were given. This afforded an opportunity to compare directly the fluid and salt restriction program with the Schemm regimen. It came about that many patients responded favor-

ably to the three gram salt diet and restricted fluids, with disappearance of all their edema, and were thus lost to further study, since they improved beyond the point where we would be able to detect additional improvement with a change in program. We were of the opinion that it was more convincing, however, to analyze the data of a few patients in whom both regimens had been observed than to institute the Schemm regimen at once on admission where the effects of bed rest and diuretics could not be separated from the regimen being tested. We can find no evidence that this had been done in the earlier investigations relating to this regimen.

In every instance the average daily urine output during the period in which the patient was taking large amounts of water failed to approach the amount of the daily fluid intake. In several of the patients who gained weight on the high fluid intake, the urine output was considerably below the intake of fluid. In no instance was there evidence that diuresis occurred, although in Case 5 the daily urine output approached a higher figure than in other patients. A requisite for success with the Schemm regimen would appear to be adequate renal function to supply a urine output approaching, equalling, or exceeding the daily fluid intake.

In five patients (Cases no. 2, 3, 4, 8, 9) oral fluid intakes in excess of 3000 c.c. were taken with difficulty, often interfering with a full consumption of the diet. In only two patients (Cases no. 1 and 5) were large fluid intakes tolerated for any length of time without complaint.

In two patients (Cases no. 1 and 6) the response to mercupurin while the patient was still on the Schemm regimen was excellent. In both instances more than 8000 c.c. of urine were excreted in a 24 hour period following an intravenous injection of mercupurin. In Case 3 a course of mercupurin while the patient was still on the Schemm regimen yielded poor results. In this patient marked chronic passive congestion of the kidneys was demonstrated at autopsy examination. The effect of the prolonged congestion on the excretory function of the kidneys can only be conjectured here, but Rowntree and his associates¹² have described decreased excretion of sodium chloride in experimentally produced chronic passive congestion, and recently Merrill¹³ has demonstrated a decreased renal blood flow in patients with chronic congestive heart failure, attributing the retention of salt resulting in edema to a low filtration rate associated with the reduced renal blood flow. Similar observations on the effect of a decreased cardiac output in chronic decompensation producing impairment of renal function and consequent faulty salt excretion have been made by Warren and Stead.¹⁴

In about half of our cases, complications, either antedating or arising during the period of observations, interfered materially with a prolonged trial of the Schemm regimen. The most troublesome of these was ascites. In all the patients who were observed ascites failed to respond to a high fluid intake, and it was usually aggravated. Ascitic fluid proved to be the most difficult manifestation to remove, and the last to disappear when diuresis induced by mercupurin was attempted.

The evidence seems clear concerning the value of a low sodium diet in the elimination of edema of cardiac origin, but clear-cut evidence has not been presented that the intake of fluid can be neglected. Our observations in the cases now being presented demonstrate the difficulties encountered in the use of the Schemm regimen and the lack of benefit in the patients we have observed when they are given a high fluid intake in the presence of congestive heart failure. From these observations we see no reason to alter the accepted program in the treatment of patients suffering from congestive heart failure, namely the use of low salt diet, restriction of fluid intake to around 1200 c.c. daily, and the use of digitalis, mercupurin and ammonium chloride. We are of the opinion that the indiscriminate use of high fluid regimen may be harmful in the treatment of heart failure. To advocate this course at this time may lead to a sense of security in the treatment of heart failure which the available data do not warrant.

SUMMARY AND CONCLUSIONS

1. The diuretic effect of the Schemm regimen, consisting of a high fluid intake and a low sodium, neutral or acid ash diet, was analyzed in nine patients suffering from congestive heart failure. Thirty additional patients were not used in the final analysis because they lost the signs and symptoms of heart failure during the control period, or because of the occurrence of events while on the Schemm regimen which invalidated inferences about the usefulness of the regimen.

2. Of nine patients, eight failed to have a beneficial effect when the regimen was used alone without the addition of mercurial diuretics in conjunction with the high fluid intake. In three patients no clinical improvement and no change in weight occurred. In six trials in six patients there was gain in weight, and fluid accumulations appeared to increase. In one patient with minimal edema, weight loss occurred, although definite clinical improvement was not apparent.

3. The average daily fluid intake for each patient ranged from 3000 to 5000 c.c. Five patients experienced difficulty taking this amount. Discomfort from the large water intake, or interference with consumption of the diet, constituted the major difficulties. Two patients experienced no difficulty with the high fluid intake, and there were no instances of untoward reactions.

4. The low sodium, acid ash diet formulated by Schemm was not liked by the majority of the patients. They considered it inferior to the standard three gram salt diet in palatability and choice of food. The limited selections of fruits and vegetables were the main undesirable features.

5. Isolated instances of marked diuresis were encountered when mercupurin was used in conjunction with the Schemm regimen. This was followed, however, by fall in the urine output to its lower levels, and in the long run the removal of fluid was not materially affected. In general the re-

sults obtained with the use of mercurial diuretics in association with the regimen were not sufficiently uniform or consistent to give the impression that mercurials were more effective when used in conjunction with this regimen than with the low salt-low fluid regimen.

6. In all patients in whom the Schemm regimen failed to produce a satisfactory response, it was observed that the daily urine output failed to approach the amount of the fluid intake.

7. Many cases were found unsuitable for trial with the Schemm regimen. Of 30 cases originally studied, only nine could be considered suitable for analysis, and of these at least half developed complications which interfered at some time with the proper maintenance of the regimen. Ascites proved to be the most difficult manifestation of heart failure to treat.

8. Seven of the nine patients fared better on the usual regimen of restricted salt and limited fluids with frequent administration of mercupurin, than they did on the Schemm regimen when fluids were forced and no mercurial diuretics were given.

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CLINICAL ASPECTS OF CARCINOMA OF THE CECUM AND ASCENDING COLON: REPORT OF 60 CASES *

By CHARLES H. BROWN, M.S., M.D., JAMES R. COLVERT, M.D., and
BROCK E. BRUSH, M.S., M.D., *Detroit, Michigan*

INTRODUCTION

CARCINOMA of the cecum and ascending colon is commonly believed to produce symptoms of anemia, diarrhea, and alternating diarrhea and constipation. Recently we have observed several cases of carcinoma of the cecum and ascending colon that did not fit into the classical picture, but had symptoms of obstruction and pain. Symptoms of obstruction and pain are supposedly not common symptoms of malignancy in this region of the colon. This has prompted us to review and correlate with the literature the clinical findings in 60 cases of carcinoma of the cecum and ascending colon. It is not the purpose of this paper to review the extensive literature on carcinoma of the cecum and ascending colon with reference to operative procedures.

CLINICAL MATERIAL STUDIED

Cases of carcinoma of the cecum and ascending colon observed at the Henry Ford Hospital from 1930-1945 are included in this study. Carcinoma of the hepatic flexure and transverse colon were not included. All cases were proved at operation. In the same period, three cases of other tumors of the cecum and ascending colon were observed, and brief comment will be made on these.

I. CLINICAL FEATURES

The age distribution in this series (table 1) is in general agreement with previous reports. Feldman¹ reports that carcinoma of the colon is

TABLE I
Age and Sex Incidence in Carcinoma of the Cecum and Ascending Colon

Age	Males	Females	Total
30-39	3	0	3
40-49	7	3	10
50-59	14	8	22
60-69	6	9	15
70-79	5	4	9
80 and over	1	0	1
Totals	36	24	60

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From the Gastro-Intestinal Division of the Department of Medicine, and the Division of General Surgery of the Department of Surgery, Henry Ford Hospital, Detroit, Michigan.

most common in the fifth and sixth decades and is comparatively rare under the age of forty. This is in agreement with our series since 62 per cent of our cases occurred between the ages of 50 and 69 years. Karsner and Clark² report that the greatest incidence of carcinoma of the cecum and ascending colon is between 40 and 60 years of age. However, both Karsner and Clark² and Ewing³ state that there have been numerous cases of carcinoma occurring in the twenties and even in the teens, and both quote a number of such instances. While none of our cases were younger than 30 years of age, it must be kept in mind that carcinoma of the large intestine may occur at any age.

The sex ratio in this series (60 per cent males) is also in general agreement with the literature. Karsner and Clark² found males more often affected than females. Bockus⁴ also states that carcinoma in this region of the bowel is more common in males.

The location of the lesions in our series was cecal in 35 cases, and in the ascending colon in 25 cases. In 11 of the cases the growth involved the ileocecal valve.

TABLE II
Presenting Symptoms in Carcinoma of the Cecum and Ascending Colon

Symptom	Number Cases	Per Cent
Pain	46	76%
Lower abdominal and RLQ	36	60%
Cramps and colic	23	38
Epigastric	7	12
Umbilical	3	5
Nausea	18	13
Vomiting	13	21
Diarrhea	12	20
Weakness	9	15
Flatulence	9	15
Loss of weight (complaint)	8	13
Constipation	8	13
Mass (complaint)	7	12
Blood in stool (complaint)	6	10
No Symptoms		
Operated upon for other causes	5	8
Mass found on routine exam.	4	7
Persistent anemia (complaint)	1	1.6

The presenting symptoms in our series of cases are tabulated in table 2. It will be seen that pain was the most common presenting complaint, being present in 76 per cent of cases. This is in agreement with Bockus⁴ who states that "Some type of abdominal discomfort or distress is present in at least 75 per cent of the cases." Karsner and Clark² found that pain was present in 14 out of 16 cases. Lahey,⁵ reporting 100 cases of carcinoma of the right colon, found that 86 per cent of his patients had abdominal cramps and/or pain. It is to be noted that the pain consisted of cramps and colic in 38 per cent of our patients; this would suggest some degree of intestinal obstruction in these patients. Pain may be of three types: (1) *that due to varying degrees of intestinal obstruction*, (2) *that due to local inflammatory*

reaction, and (3) that caused by invasion of the peritoneum and surrounding structures.

Vomiting was present in 13, or 21 per cent, of our cases. Nausea was present in eight cases or 13 per cent. *These symptoms and some of the symptoms of pain were undoubtedly due to intestinal obstruction*, a finding that is considered to be relatively rare in carcinoma of the cecum and ascending colon.

Diarrhea, a supposedly common symptom in this condition, was present in only 12 cases or 20 per cent. Karsner and Clark² found only five out of 16 cases had diarrhea. No patient in our series gave a history of alternating diarrhea and constipation. Constipation was present in eight cases or 13 per cent. Bockus⁴ states that approximately 25 per cent of the patients with carcinoma of the right colon complain of constipation.

Six patients complained of blood in the stool. Three patients out of 16 in Karsner and Clark's² series had this same complaint. In only one patient was persistent anemia a *complaint*. Weakness was present in nine patients or 15 per cent. This is in rough agreement with Bockus⁴ who states that weakness is present in about one fourth of these cases.

Another diagnosis was made in five of our cases pre-operatively at this hospital. These cases will be discussed under diagnosis.

Three of our patients had been operated upon elsewhere three months prior to coming to this hospital. Two had had appendectomies, and one a cholecystectomy. Mayo⁶ reports that 15 per cent of the cases of carcinoma of the right colon undergo appendectomy after the onset symptoms.

TABLE III
Duration of Symptoms before Operation

Time	No. of Cases
Less than 1 month	8
1-3 months	20
3-6 months	17
6-9 months	9
9-12 months	11
Over 12 months	7

From table 3 it can be seen that symptoms are often present for a considerable length of time before operation. The average duration of symptoms before surgery was six and one-half months. This is in agreement with the findings of others. Allen and Welch⁷ found an average delay of eight months before operation. Harms et al.⁸ ascribe this delay as follows: 45 per cent due to the patient, 25 per cent due to the physician, and 30 per cent due to both. This delay is often due to the patient neglecting his own symptoms. It frequently results from neglect on the part of the physician in not carrying out adequate diagnostic studies, or in not repeating these studies should symptoms persist while the patient is under treatment.

While only 13 per cent of the patients in this series complained of weight loss, 70 per cent of them had a weight loss of over 10 pounds, and 37 per cent

had a weight loss of over 20 pounds. The weight loss in general increases with the duration of the symptoms and is quite marked when signs of obstruction or severe pain have developed. Table 4 shows the weight loss in our cases.

TABLE IV

Loss of Weight in Carcinoma of the Cecum and Ascending Colon

Pounds Lost	No. of Cases
No weight loss	6
1-9 pounds	6
10-19 pounds	20
20-29 pounds	10
30-39 pounds	6
40 pounds and over	6
No data	6

Connor and Harvey⁹ recently reported that a palpable mass was found in 82 per cent of their cases on first examination. In our series, a mass was palpated in 38 or 63 per cent of the cases at the time of the first examination. A palpable mass was the presenting *complaint* in seven patients; and a palpable mass was found in four patients who had no symptoms but who came in for a routine examination.

The presence of anemia in cases of carcinoma of the cecum and ascending colon has frequently been stressed by many authors. Bockus⁴ states that approximately two thirds of the patients with lesions in the right colon have anemia. It is certain that in an unexplained anemia, carcinoma of the cecum and ascending colon should be considered. In our series 79 per cent had a hemoglobin of less than 13 grams, but 46 per cent had a hemoglobin greater than 11 grams. Most of the cases with anemia had had symptoms for over six months and also showed a marked loss of weight.

TABLE V

Hemoglobin in Cases with Carcinoma of the Cecum and Ascending Colon

Grams of Hemoglobin	No. of Cases
Under 7 grams	6
7-8.9 grams	7
9-10.9 grams	18
11-12.9 grams	14
over 13 grams	12

In this series of cases, on the first examination for occult blood in the stools the results were 15 negative and 37 positive. In five of the 15 cases with no occult blood in the stool at the first examination subsequent examination gave positive results. Bockus⁴ states that it is rare for carcinoma of the large intestine not to be associated with occult blood in the stool.

II. DIAGNOSIS

It can be seen from the foregoing that the diagnosis is often made only after the malignant lesion has existed for some time. The long duration

of symptoms prior to operation, the high per cent that have a mass present when the diagnosis is made, the number of patients who have loss of weight and obstructive symptoms, and the other cases in which the diagnosis is made only in the operating room indicate that the diagnosis is often long delayed.

It has been pointed out in the preceding section that three of our patients had had operations done elsewhere (two appendectomies and one cholecystectomy). This has occurred in 15 per cent of the cases of carcinoma of the right colon seen at the Mayo Clinic.⁶

Unexpected tumors of the cecum and ascending colon were found in our series at operation in five cases in which the following pre-operative diagnoses had been made: Ovarian cyst, two cases; appendicitis, two cases; elective hysterectomy, one case.

The two cases in which appendicitis was diagnosed preoperatively both had perforation of the cecum. Brown¹⁰ states that "Tumors in the proximal colon may cause symptoms closely simulating appendicitis, and in several cases in this series the carcinoma was only discovered after laparotomy had been performed for a supposed chronic appendicitis." From the above, and from the presenting symptoms shown in table 1, it is understandable how carcinoma in this area can be confused with other conditions causing pain in the right side of the abdomen.

One should make a thorough investigation, including a barium enema study, of patients presenting any of the symptoms listed in table 2. If a first barium enema is negative and the symptoms persist while the patient is under treatment, the x-ray examination should be repeated after a short time.

In a previous paper we presented the results of barium enema examination in patients with carcinoma of the cecum and ascending colon.¹¹ The correct diagnosis was made in 72 per cent of the cases on the first examination. An additional 20 per cent required a repeat barium enema examination before the diagnosis could be made. Even with good preparation and a negative barium enema study, the examination should be repeated in a short time if there is clinical evidence suggesting a malignant lesion in this area.

III. PATHOLOGY

The pathological findings are presented in table 6. Numerous classifications and descriptions of carcinoma of the colon have been used. Stout's¹² classification is used here. Associated pathological conditions and further description of the lesion are also presented.

It will be noted from table 6 that 28 of our cases had a nodular lesion. This frequently was ulcerating and had a fungating appearance. Twenty of our cases had a scirrhous type lesion, with the growth infiltrating the bowel. In these 20 cases, two were definitely signet ring in character. Bockus⁴ states that this type of carcinoma is relatively uncommon in the colon and is found more often in the left than in the right colon. Eight or 13 per cent of our cases had a colloid carcinoma. Rankin and Chumley¹³ found colloid

carcinoma to be relatively uncommon and to constitute only about 5 per cent of the carcinomas of the large bowel. However, since the cecum is one of the favorite sites for colloid carcinoma, the higher percentage of this type in a series restricted to carcinoma of the cecum and ascending colon is to be expected. Only two cases were papillary. This is to be expected since papillary carcinoma is more common in the rectum than elsewhere in the large bowel.

TABLE VI
Pathology and Associated Pathology in Patients with Carcinoma of the Cecum and Ascending Colon

Pathology	No. of Cases	%	Associated Pathology	No. of Cases	%
Nodular	28	47	Ulcerating	23	38
Scirrhouous	20	33	Constricting and obstructive	15	25
Signet ring	2	3	Annular	19	32
Colloid	8	13	Polyposis of colon	2	3
Papillary	2	3	Perforation of cecum	2	3

Twenty-three of our cases presented ulcerated lesions: most of these had the nodular type of carcinoma. Nineteen patients had an annular lesion. This type of lesion is supposed to be uncommon in carcinoma of the cecum and ascending colon. However, Craig and MacCarty¹⁴ in a study of lymph gland involvement in cases with carcinoma of the cecum found that 43 per cent of their series had an annular carcinoma. They also found that the ileocecal valve was involved in 64 per cent of the cases of carcinoma of the cecum. With the ileocecal valve involved, and with an annular lesion, one would expect to find symptoms of obstruction even though the feces were liquid at this point. Burgess¹⁵ found 14 cases of 25 cases of carcinoma of the cecum and eight cases of 11 cases of carcinoma of the ascending colon were associated with acute intestinal obstruction. *Fifteen or 25 per cent of our cases showed signs of obstruction.* This is compatible with our analysis of symptoms, in which we found a number of patients had symptoms of obstruction with pain, cramps, colic, nausea and vomiting. From our series, the series of Burgess,¹⁵ and the series of Craig and MacCarty,¹⁴ it can be seen that obstruction rather than being an uncommon pathological finding in carcinoma of the cecum and ascending colon is relatively common.

It is to be noted from table 6, that two patients had perforation of the cecum and two patients had associated polyposis of the colon. One patient with carcinoma had an intussusception.

The microscopical grading in our cases was as follows: Grade 1, three cases; Grade 2, 25 cases; Grade 3, 11 cases; Grade 4, three cases; and ungraded, 18 cases.

In reviewing this series of cases, three patients with other tumors of the cecum were found. One of these had an intussusception caused by a *lipoma*. One other patient had a mildly malignant *carcinoid* tumor of the cecum. Waugh and Snyder¹⁶ found only 12 recorded cases of carcinoid tumor of the colon. The carcinoid tumor in our group was definitely in the cecum and

did not arise from the appendix. The third patient had a large benign adenoma.

IV. TREATMENT AND PROGNOSIS

The operative mortality of carcinoma of the cecum and ascending colon is influenced by the fact that these tumors may be first discovered during the course of another operation such as a pelvic operation or an appendectomy. Three cases in this group were thought to have ovarian lesions, while two cases were operated upon for appendicitis after perforation of the cecum. In three other patients an operation had been performed elsewhere within three months. The operative mortality is also affected by the fact that patients with these lesions and in this age group not infrequently have cardiovascular-renal disease. One of our patients died post-operatively of uremia. The long duration of symptoms of the patients also influences the operative mortality. The use of the Miller-Abbott tube, sulfa preparations and penicillin have become important factors in the management of these cases. The operative mortality in this series is shown in table 7. It will be noted that with the advent of the Miller-Abbott tube, sulfasuxidine and sulfathaladine, and penicillin the operative mortality has fallen from 21 per cent and 23 per cent to 8 per cent. This 8 per cent (two cases in 24) includes one patient who was in poor condition and died post-operatively with a high blood non-protein nitrogen and uremic symptoms. The second case died following colostomy and did not have a resection.

TABLE VII
Post-Operative Mortality

Time	No. of Cases	No. Died	% Mortality
Prior to 1937	13	3	23
1937-1942	23	5	21
After 1942	24	2	8

The spread of carcinoma to the regional lymph nodes seriously endangers that patient's chances of permanent recovery. In the patients with involved glands at the time of operation only 29 per cent survived a four year period following operation. In our patients who had no evidence of metastases at operation, the four year follow-up revealed that 71 per cent survived this period.

The location of metastases was as follows: regional lymph nodes, 27; liver, 9; pelvis, 3; lungs, 1.

TABLE VIII
Presence of Metastases *

Absent in	33 cases	71% survived	average follow-up of 3.8 yrs.
Present in	27 cases	29% survived	average follow-up of 4 yrs.

* Since some of these patients were operated on in 1944 and 1945 we do not have a five year follow-up on the complete series.

It seems apparent that usually carcinoma of the cecum and ascending colon must be relatively slow growing. The duration of the symptoms averaged six and one-half months, but metastases were present in less than half the cases. Even with metastases present, the outlook is not hopeless, since 29 per cent of this group survived a four year period. One patient who had neighborhood gland metastases is enjoying good health 10 years after operation.

SUMMARY

Sixty case histories of carcinoma of the cecum and ascending colon have been analyzed. Pain was the predominant presenting symptom, being present in 76 per cent of the patients. Many patients had symptoms of obstruction, with cramps and colic (38 per cent) and vomiting (21 per cent). Diarrhea was present in only 20 per cent of our cases. The average duration of symptoms before surgery was six and one-half months. Seventy-nine per cent of the patients had an anemia with less than 13 grams hemoglobin, but only 54 per cent had less than 11 grams.

Pathologically the most noteworthy findings were that 32 per cent had an annular type of growth and 25 per cent had a constricting and *obstructive* lesion.

The immediate post-operative mortality in the last five years has been 8 per cent, two of 24 cases. One of these two cases was a poor renal risk and died from postoperative uremia. Seventy-one per cent of those cases with no evident metastatic lesions at operation were surviving on an average follow-up of 3.8 years. Twenty-nine per cent of those with metastatic lesions were surviving on an average follow-up of four years.

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THE COURSE OF BERIBERI HEART DISEASE IN AMERICAN PRISONERS-OF-WAR IN JAPAN*

By RUSSELL J. ALLEMAN,† Maj., M.C., A.U.S., and GENE H. STOLLERMAN,‡ Capt., M.C., A.U.S.

THE literature in recent years on the cardiovascular complications of thiamin deficiency has made it more and more evident that the syndrome of "Beriberi Heart" is not limited to the classical features emphasized in the studies of Aalsmeer and Wenckebach^{1,2} but is subject to great variation in clinical manifestations, pathology and course. The striking variability in the course of Oriental "wet beriberi" impressed even the earlier investigators of the disease. Vedder³ in 1913 in describing the clinical picture wrote: "None of the descriptive classifications are strictly accurate. The case which apparently belongs in the rudimentary or undeveloped type may . . . develop cardiac symptoms and die suddenly. . . . Again, cases of moderate severity belonging to dry or wet types who are under treatment in hospitals and apparently progressing favorably may suddenly sit up in bed and die most unexpectedly of cardiac failure. The rudimentary form may remain in this incompletely developed condition for months or even years . . . with periods of slight improvement or exacerbation but without material change."

Wenckebach⁴ was struck with the picture in his Javanese cases of acute cardiac decompensation with dilated right heart, venous engorgement, signs of a rapid circulation, pistol-shot arterial sounds, rapid, bounding pulse, a picture similar to the circulatory dynamics of arteriovenous aneurysm. He emphasized the pathological features of enormous dilatation of the right heart, engorged proximal and hepatic veins, and, microscopically, hydropic degeneration of heart muscle and fibrosis of the myocardium. He explained this picture on the basis of (1) arterial dilatation and (2) a weakened myocardium incapable of dealing with increased venous return.

The report of Scott and Herrmann⁵ of "maladie des jambes" in Louisiana stimulated further interest in beriberi in this hemisphere. The extensive studies of Weiss and Wilkins,^{6,7,8} and of Goodhart and Jolliffe,^{9,10} of beriberi in chronic alcoholics broadened the concept of the clinical picture of thiamin deficiency in this country. As a result of their studies it was concluded by Weiss and Wilkins that the cardiovascular disturbances caused by nutritional deficiency do not form a single rigid clinical syndrome. Not all cases show the characteristic right heart enlargement and manifestations of a rapid circulation. Even the response to therapy, considered one of the most constant criteria in diagnosis, is not absolute. Weiss⁷ notes that on rest and dietary regime circulatory disturbances disappear rapidly in one

* From the medical service of Percy Jones General Hospital, Battle Creek, Michigan.
† Cardiology consultant.
‡ Chief of Section, Medical Service.

group and slowly in another, the duration and severity of deficiency being important, and that thiamin deficiency when chronic, is followed by secondary changes of slow reversibility. Cardiac dilatation, hypertrophy, hydropic degeneration of myocardial fibers and increase in collagen are evidence of myocardial damage, not simply myocardial edema. Since the pathological histology observed is not specific or characteristic, Weiss set up the following criteria for diagnosis: (1) Dietary history, (2) response to treatment, (3) simultaneous presence of other manifestations of deficiency, (4) absence of other etiology for heart disease, (5) electrocardiographic changes disappearing after therapy and (6) similarity of clinical syndromes and histological findings in the heart to those observed in beriberi elsewhere in the world. It has been further pointed out that the clinical manifestations of cardiovascular disease may not even be apparent and that electrocardiographic changes have been observed in the "pure type" of polyneuritis (dry beriberi). Also, changes in the heart can develop independently of the other recognized clinical signs of B deficiency.⁷

More recently Blankenhorn¹¹ has still further extended the criteria for the diagnosis of beriberi heart disease. He asserts that undue emphasis on the traditional criteria will exclude many cases from recognition and treatment. When such material as can be found in the recent literature is tested by these traditional criteria, very few cases conform. "It appears that beriberi heart disease is both a myocardial disorder and a disease of the nervous system and comprises no rigid syndrome." He offered the following diagnostic criteria: (1) Enlarged heart with normal rhythm, (2) dependent edema, (3) elevated venous pressure, (4) peripheral neuritis and pellagra, (5) non-specific changes in the electrocardiogram, (6) no other causes [for heart failure] evident, (7) gross deficiency of diet for three months or more, (8) improvement and reduction of heart size after specific therapy, or autopsy findings consistent with beriberi. Moreover, he also states "we do not consider the failure to improve with thiamin treatment as proof that beriberi is to be excluded" and cites a case to confirm this contention.

This opinion has also been supported by Vilter¹² who avers that the classic syndrome of Wenckebach is of less frequency than the beriberi heart disease that resembles degenerative heart disease of other etiology. He reviewed 11 cases of which almost all had a history of dietary deficiency, peripheral neuritis, enlarged hearts, elevated venous pressure with edema, electrocardiographic findings of low voltage and T-wave changes, and a decrease in heart size. In those cases which recovered on thiamin therapy, only one showed dramatic water loss and compensation. Recovery usually occurred over several weeks and this was considered compatible with beriberi heart disease in which there had been some irreversible myocardial damage.

With this expansion in the criteria for diagnosis, it is not surprising that in some recently reported cases of chronic myocardial damage of unknown etiology, a dietary deficiency factor should have been carefully investigated as the possible cause. Dock¹³ in 1940 presented a series of cases of unex-

plained congestive heart failure with recurring dyspnea and embolic accidents which showed marked cardiac hypertrophy and mural thrombosis. In these cases careful history established definite dietary deficiency and no other causes for heart disease could be uncovered. Dock commented on the great variety of clinical and pathological findings in beriberi depending upon the region and type of patient studied. "It is probable that conditions found in beriberi will vary depending on the degree of fatigue and muscular effort experienced by patients, . . . on the degree of over or under nutrition . . . and whether deficiency is acute, chronic or intermittent." Some of his cases responded to vitamins and diet for as long as two years, only to decompensate again due to poor eating and heavy work.

Smith and Furth¹⁴ also raise the question of the rôle of dietary deficiency in their five cases of fibrosis of the endocardium and myocardium with mural thrombosis, and of the relationship of chronic beriberi heart to Fiedler's myocarditis. Hussey and Katz¹⁵ from a study of their cases (which, like Dock's, developed pulmonary emboli) conclude that the symptoms and signs of beriberi heart disease show no important variation from those of heart failure due to other causes and therefore the diagnosis depends mainly upon securing evidence of deficient diet, ruling out other etiologic types, and on the therapeutic response to the administration of vitamin B. Even the last is not considered absolute by these authors since in some cases response to the therapeutic test was delayed or poor and this result did not seem to them to rule out the diagnosis of beriberi heart disease. Toreson¹⁶ reported still another case of diffuse isolated myocarditis associated with dietary deficiency, resembling those of Smith and Furth, and raised the question whether the myocardial changes represent a variant of beriberi heart. His case made an excellent response to thiamin and diet but on a later hospital admission failed to recover despite large doses of thiamin.

This experience with the variability in the course and therapeutic response of thiamin-deficient hearts is characteristic of oriental as well as of occidental beriberi. Kuo¹⁷ in 1939, reviewing his cases of beriberi in China, found a variable clinical and pathological picture of heart failure in agreement with the studies of Weiss and Wilkins. While all of Kuo's cases responded to thiamin, he states that "The importance of prolonged after-care, as in other cardiac diseases, is a problem to be solved only by repeated instructions to the patients. . . . With the best of care, however, we find a few cases coming back to us with relapses which may prove fatal . . . a most important point in therapy is absolute rest and dietary measures. The period of absolute rest in bed varies with each individual case and his reaction to gradual exercise and exertions. Careful and repeated instructions are given to all patients on discharge but . . . the results have been rather discouraging."

From the foregoing it is apparent that in the minds of many the concept of the cardiovascular complications of thiamin deficiency is one of a diverse picture of cardiac insufficiency and that the diagnosis rests on singularly few reliable criteria. Lacking the usual classical features of the disease, the two

remaining criteria which make a thiamin-deficient myocardium at least a possible diagnosis are (1) a picture of cardiac insufficiency unexplained by other etiological factors and (2) a history of a thiamin-deficient diet.

The following two cases reported are selected from a small group of patients studied in this hospital who had typical beriberi as American prisoners-of-war in Japan. These cases present a striking contrast in the course of beriberi heart disease in two men who suffered under almost identical conditions for the same length of time and showed an almost identical clinical picture initially. The first case is of particular interest relative to the foregoing remarks on the variety of clinical syndromes and the broadening concept of diagnostic criteria for thiamin-deficiency cardiovascular disease. He presented in succession the classical chronic, oriental, "wet beriberi"; two relapses, after apparent recovery, into the acute form of edema and cardiac decompensation; and finally the stage of very slow recovery similar to other forms of chronic myocardial insufficiency. The second case by contrast represents an apparently complete clinical recovery in spite of a well developed, prolonged and typical "wet beriberi."

CASE REPORTS

Case 1. The patient is a 28 year old white male. He entered the army in November 1941 in excellent health and had no past or family history of cardiovascular or renal disease. While serving in Java, he was captured by the Japanese on March 12, 1942 and was held as a prisoner-of-war for 43 months. During his internment, most of which was in Japan, he subsisted on a grossly inadequate diet and was compelled to perform heavy labor. For the first 12 months the diet consisted of two bowls of polished rice daily, tea, and occasionally a watery vegetable soup. He received no meat and had fish on but five occasions during his entire imprisonment. The last six months of his internment, barley was generally substituted for rice.

About eight months after being taken prisoner the patient began to develop cracking of the lips and sores in and about the mouth. His tongue became dry, swollen and painful. He gradually developed a massive pitting edema of the legs, arms and face, so that at times his extremities reached twice normal size and his ears "swelled up big as fists." He noticed that he became increasingly short of breath with exertion and developed severe cramps in his calves. At night while lying down he was orthopneic and noted a rapid "bounding" of his heart. He had difficulty in controlling and coordinating the movements of his legs. Toward the end of the first year his skin became rough and dry and a bluish-black discoloration appeared about the wrists, ankles and dorsum of the feet. Increased tendency to bruise was noticed and bleeding of the gums was common. He lost over 40 pounds. In spite of his condition he was forced to do heavy work in mines and shipyards until liberation. Toward the end of the war, the prisoners were fed by food dropped from "mercy B-29's." This food was predominantly carbohydrate, consisting of sweetened evaporated milk and chocolate. It was noted by the patient, as well as the other P.O.W.'s, that there was marked exacerbation of their symptoms, especially the edema, following the acutely augmented carbohydrates.

The patient was liberated October 1945. When he reached San Francisco in December 1945, he had gained 40 pounds and had only slight edema of the legs. He states that he felt quite well, except that most of his weight gain was in loose fatty tissue around the torso and abdomen and he was still weak. He was sent to Schick General Hospital at Clinton, Iowa, for further nutritional rehabilitation. Because

of the patient's lack of complaints and absence of clinical findings he was given frequent passes and furloughs. During this time away from the hospital he admits to a heavy alcoholic intake often at the expense of an adequate diet. In addition he developed vagaries in his appetite and would eat only one food, such as canned tomatoes, for a week or so at a time. In February 1946 he went home on furlough. While at home he continued to consume alcohol excessively and to eat erratically. On May 10, 1946 he suddenly developed dyspnea, nausea, vomiting, massive edema of face and extremities, and swelling of the abdomen. His weight increased 25 pounds in a few days and because of his critical condition he was flown to the Veterans Hospital at Fargo, N. D.

On admission he was in acute congestive heart failure with massive anasarca. His temperature was 101°, respirations 34 and pulse 155. There were no obvious stigmata of vitamin deficiencies. His heart was enlarged on examination, with a gallop rhythm and no murmurs. Coarse râles were found at both bases. The liver was enlarged and tender. The blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. Laboratory findings revealed mild anemia, normal white count, normal urinalysis with no albuminuria, and a mild hypoproteinemia. The chest roentgenogram demonstrated marked cardiac enlargement and passive congestion of the lungs (figure 1, A). The electrocardiogram showed low voltage and an inverted T in CF₄. He was immediately treated with thiamin and large parenteral doses of B-complex but in view of the severity of his heart failure, it was considered advisable to use all other available measures and he was therefore also given salyrgan, oxygen and digitalis and kept on strict bed rest and a salt-free diet. The response to treatment was dramatic with an immediate diuresis and relief of symptoms and within three weeks the patient was ambulatory and asymptomatic. A repeated teleroentgenogram taken 20 days after treatment revealed a reduction in heart size to within normal limits (figure 1, B).

He was transferred to Ft. Sheridan Regional Hospital where intensive vitamin therapy and restricted activity were continued. Digitalis was withheld. Laboratory evaluation showed normal blood counts, urinalyses, stool examinations, basal metabolism and liver function studies. Serum proteins which were slightly low on admission soon became normal. In September 1946 he appeared fully compensated and was again sent home on furlough. On this second trip home the patient states he ate and slept "adequately," drank only "moderately" and took oral vitamin tablets. However, the patient is an active, enthusiastic individual and as a result his physical activities were not particularly curtailed.

In October 1946, about a month later, he again suddenly went into profound heart failure (figure 2, A). He was again hospitalized at Fargo, N. D. and the previous regimen repeated. The symptoms rapidly disappeared and he was again transferred to Fort Sheridan Regional Hospital and finally from there to Percy Jones General Hospital in December 1946. On admission the patient appeared well nourished and well developed, with no edema. His tongue was smooth around the edges and at the tip. Careful neurological examination revealed symmetrical hypesthesia and hypalgnesia in the ulnar, median, radial, peroneal and tibial nerve areas bilaterally, and there was sufficient evidence of trophic, symmetrical peripheral nerve involvement to warrant the diagnosis of the residua of a multiple peripheral neuritis. He had a tachycardia of 104 at rest with a presystolic gallop rhythm. Blood pressure was 90/65. The lungs were clear, and the liver was not enlarged. Venous pressure on admission was 60 mm. with an arm-to-lung circulation time of 13, and arm-to-tongue of 23, seconds. Repeated circulation time and venous pressure thereafter were always within normal limits. Vital capacity was 3.9 liters. Laboratory studies again showed a normal blood count, hematocrit, urinalysis, stool examination, basal metabolism, sedimentation rate, serum albumin and globulin, and urea nitrogen. Teleroentgenogram showed a somewhat enlarged heart which was more apparent in the left anterior

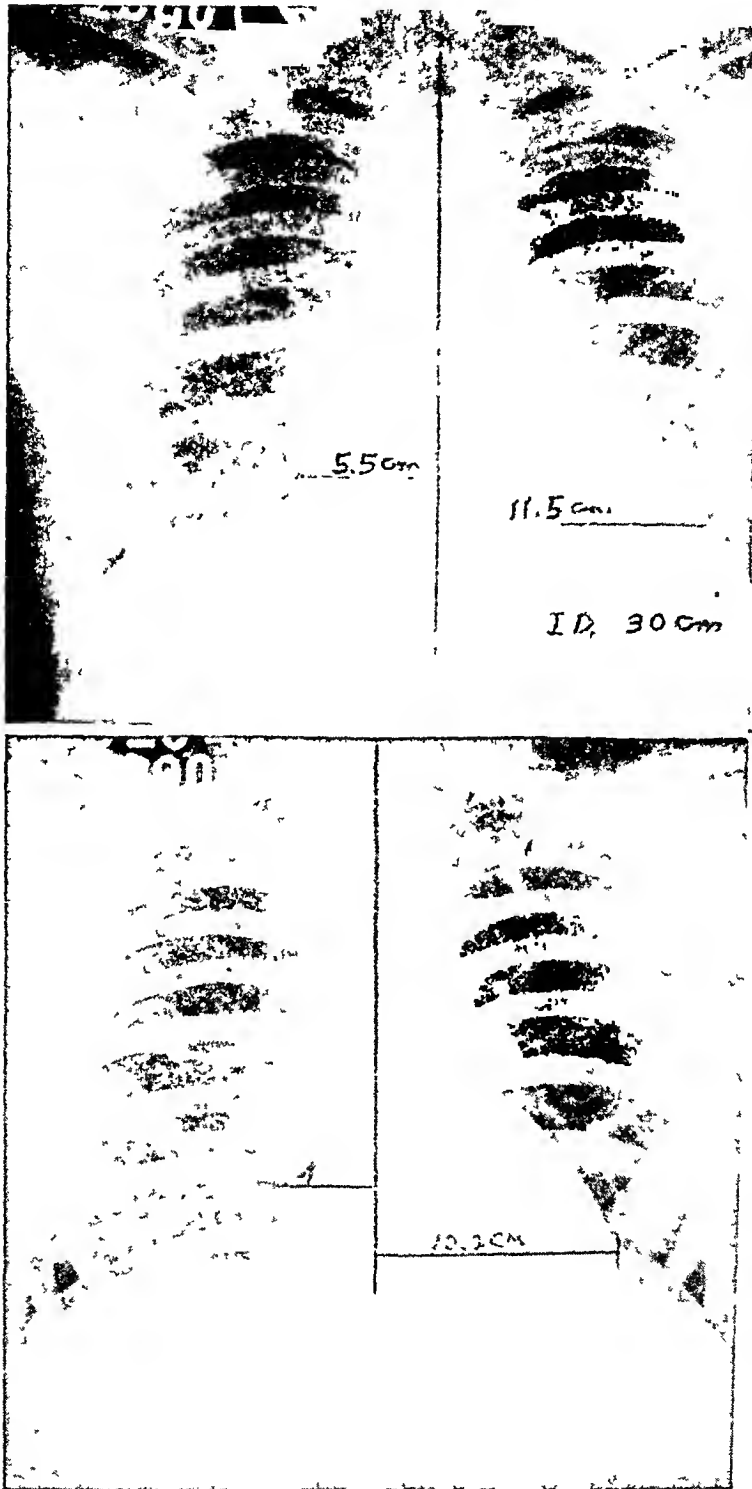


FIG. 1. Case 1. Roentgenograms of the chest demonstrating (A-above) generalized cardiac enlargement (May 27, 1946) shortly after the patient's first relapse and (B-below) the shrinking of the heart (June 20, 1946) to within normal limits 20 days after treatment was instituted.

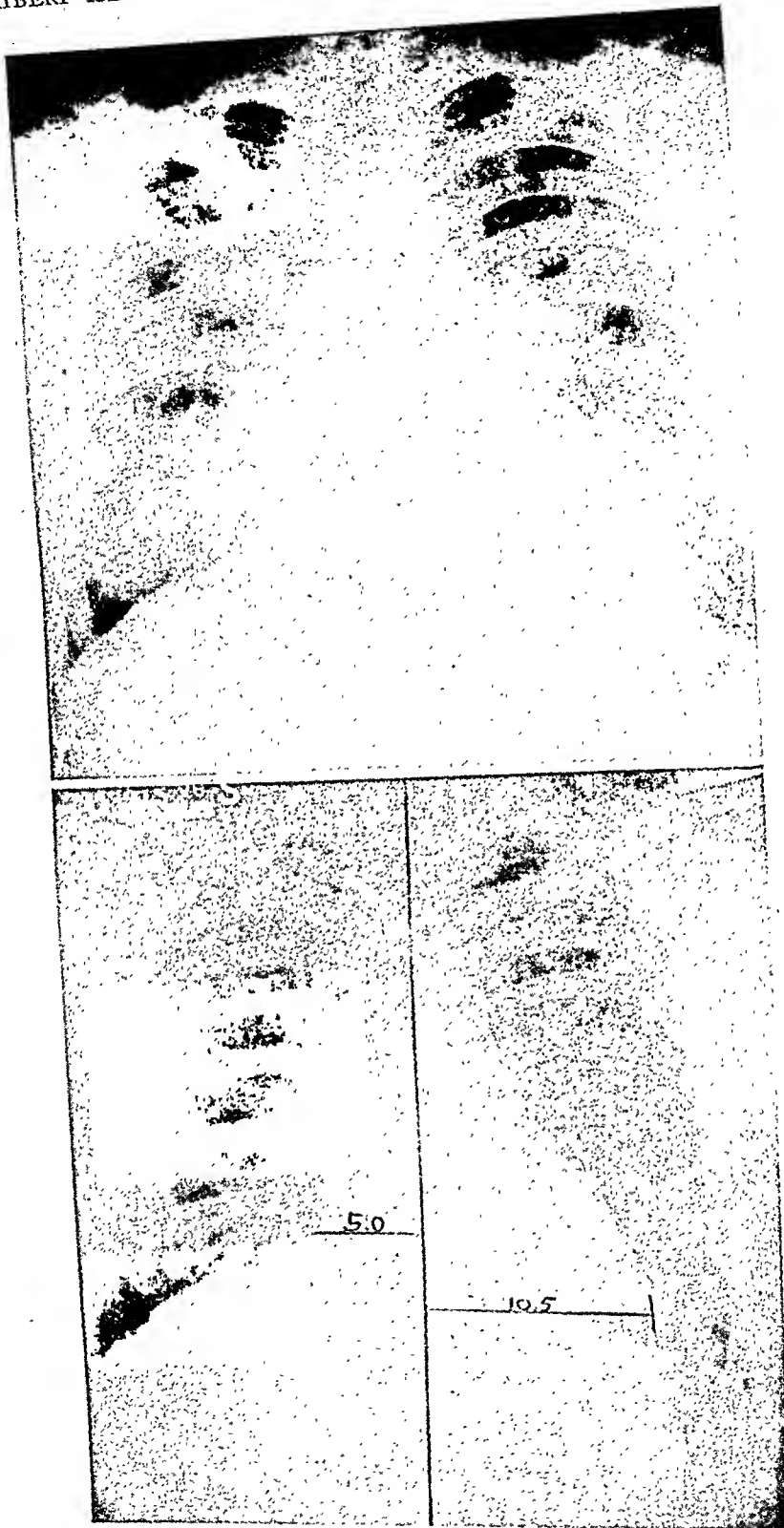


FIG. 2. *Case 1.* Roentgenograms of the chest demonstrating (A-*above*) generalized cardiac enlargement and passive congestion of the lungs (Nov. 4, 1946) taken shortly after the patient's second relapse and (B-*below*) the persistence of some cardiac enlargement (Dec. 15, 1946) after two months of treatment and bed rest.

oblique views. The electrocardiogram (figure 3) showed low voltage, inverted T-waves in CF_4 and CF_5 , and absence of R in CF_2 . Upper gastrointestinal series was normal except for some hypermotility but revealed no pattern of vitamin deficiency. However, there was a hypochlorhydria, no free acid being obtained on test meals, and after histamine a maximum free acid of 33 units.

He was placed on a regimen of strict bed rest, intensive parenteral vitamin therapy, Brewer's yeast, and a salt-free diet high in protein and carbohydrate. After several months on this regime he seems improved clinically although there has been no

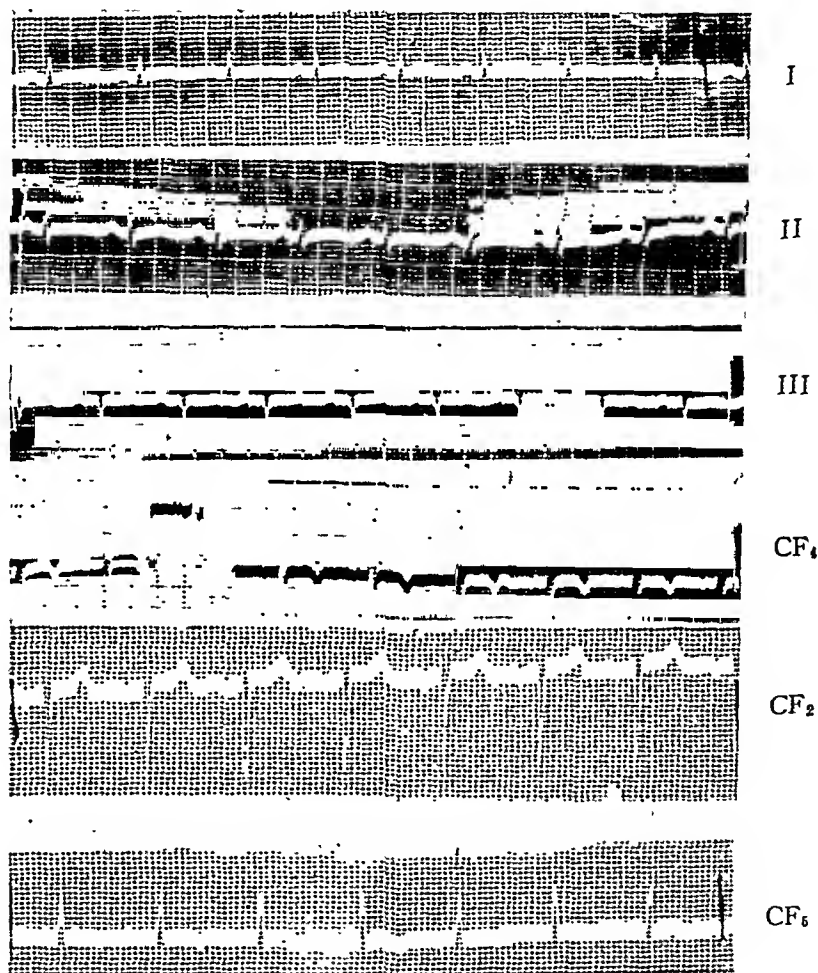


FIG. 3. *Case 1.* Electrocardiogram recorded on Dec. 15, 1946. P-R, 0.16 second, QRS, .06 second. Rate 98. Low voltage in the limb leads with left axis deviation. T-waves flat in the limb leads and inverted in CF_4 and CF_5 . Absent R-wave in CF_2 . Repeated electrocardiograms during the patient's hospitalization showed no significant changes.

change in his heart size or electrocardiographic findings. His resting pulse is now within normal limits and there is no gallop rhythm at rest. However, his myocardial reserve is limited. He has occasional paroxysmal nocturnal dyspnea, dyspnea on mild exertion and after large meals, and an exercise tolerance test shows a prolonged tachycardia after exertion. It was noted that when he was placed on oral vitamin therapy after the first month in the hospital, his tongue became sore and smoother at the tip and edges and he had more cardiac complaints. These symptoms and signs disappeared, however, when dilute hydrochloric acid was added to his meals and oral

vitamin therapy continued. It is our intention to continue this regimen for several more months before conceding that maximum therapeutic benefit has been achieved.

Case 2. The patient is a 22 year old white male. He entered the army in 1941 underage but in excellent health with no past or family history of cardiovascular or renal disease. He was captured by the Japanese at Corregidor in 1942 and was held as a prisoner-of-war for 42 months. This patient also subsisted on the meager rations and identical diet described in case 1 and was compelled to perform heavy labor in mines. After about six months of his internment he also developed the identical mouth lesions and ataxia of pellagra, the skin and mucous membrane lesions of scurvy and vitamin A deficiency, and the cardiovascular manifestations of beriberi described in case 1. He relates that he was hugely edematous and that he often pricked his legs with a pin and watched "water spurt out like a fountain" to relieve his edema. He kept cool pebbles in his mouth at night to relieve the soreness of his tongue. He suffered severe dyspnea on exertion and orthopnea and was conscious of a rapid pounding of the heart.

In 1943 he was trapped in a mine explosion and suffered a compound fracture of the left tibia and fibula. He received no medical attention except for crude splints applied by his buddies who also washed his leg wound with water. He lay in his quarters for 120 days unable to move and subsisting on one bowl of rice per day since men who could not work were placed on half-rations. His fellow prisoners exhorted him to get on his feet to regain the use of his leg and obtain his "full" rations. This he managed to do with crude crutches and after several weeks he was able to walk with a cane and return to the mines, reclaiming his two bowls of rice daily. He was finally able to discard the cane and his wound healed although the fracture was ununited.

With the dropping of food from the "mercy B-29's" toward the end of the war, this patient also had an exacerbation of symptoms. Following liberation in October 1945 this man was evacuated and treated as a bed patient most of the time because of his orthopedic problem. His diet was carefully managed and he was given large doses of oral and parenteral vitamins. His symptoms and signs of multiple vitamin deficiencies gradually disappeared and at the end of four months he was no longer edematous and no longer complained of palpitations or dyspnea.

At present the patient is at Percy Jones General Hospital where he is recovering from a bone graft of the ununited fracture. He presents no clinical evidence of vitamin deficiency. Physical examination of his heart reveals no abnormality and teleroentgenogram shows his heart size to be within normal limits. His electrocardiogram is normal. While it is impossible to test fully his myocardial reserve because of his sedentary status, he has noted no exertional dyspnea and no tachycardia is apparent on casual examinations. He continues to eat a well balanced diet with vitamin supplements.

DISCUSSION

The conditions under which the above cases, and other prisoners in the same units as these men, developed symptoms and signs of avitaminoses has the uniformity of a planned experiment. Almost all cases were young, white males with no known preëxisting cardiovascular disease; all ate an identical diet and lived under the same conditions; and all did heavy labor. It was found on careful questioning that both of our cases were intelligent and accurate observers and were able to provide us with detailed and reliable accounts of their own, as well as of their fellow prisoners', symptoms and manifestations of beriberi, pellagra, scurvy and avitaminosis A.

The fact that the first signs of thiamin deficiency began to appear after about six to eight months in almost all of the prisoners indicates a partial rather than complete B₁ deficiency in their diet. It has been frequently observed that this situation is most important for the development of neurological and cardiovascular lesions of beriberi. Cowgill¹⁸ has pointed out that in man the requirement of the vitamin varies directly with the metabolism of the body and the ingestion of carbohydrate and that for this reason inanition alone doesn't produce deficiency. Experimental evidence also strongly supports this thesis. In monkeys, chronic cardiac symptoms and myocardial lesions can only be produced by partially thiamin-deficient diets and the duration of the deficiency determines the permanence of the myocardial damage.¹⁹ The same is true of dogs and pigeons^{20, 21} and the most advanced and permanent damage is produced where feedings are high in carbohydrate and metabolism is increased. It was a common observation of both of our patients that when the prisoners were first fed with rich food dropped by "mercy bombers" as liberation approached, an exacerbation of symptoms of anasarca, dyspnea and nervousness occurred.

Another factor of utmost importance which militated for the development of cardiac damage was the enforced hard labor imposed upon all prisoners. Keefer²² has emphasized the tremendous rôle muscular exercise plays in the course of the disease. Patients with severe nerve changes and motor weakness which limits their activity may show electrocardiographic changes and enlarged hearts, but without symptoms of cardiac insufficiency and decompensation. In neither of our patients was peripheral neuritis severe enough to prevent heavy labor in mines and shipyards, although both complained of severe weakness of the legs and a peculiar lack of coördination on walking. The dramatic story of case 2's survival of a compound fracture of the tibia and fibula we believe is of definite significance in the ultimate course of his disease. The enforced, prolonged rest to which he was subjected as an orthopedic case after liberation is one of the possible explanations of his apparent complete recovery.

Case 1 in particular deserves careful analysis of the factors influencing his course in that he illustrates not only varying stages in the syndrome but many problems of treatment and management. Following his liberation he made what was superficially a complete recovery. He regained his weight and to some degree his strength and was without striking apparent signs of avitaminoses. However, he did notice that after his return to the States his appetite fell off and he had bizarre food cravings. He also confessed to a heavy alcoholic intake and in view of his apparent well-being he was allowed much freedom during which time he kept late hours and in no way curtailed his activities. He also failed to continue his vitamin therapy once he returned home. The sudden episode of acute cardiac decompensation with massive anasarca in May of 1946 is easily explained as an acute relapse of beriberi heart disease, a complication frequently warned against by many authorities.^{3, 9, 17} That this diagnosis was correct is confirmed by his rapid

recovery on therapy with a prompt decrease in the size of his heart within approximately three weeks (figure 1). It may be noted that in addition to large doses of thiamin and B complex, he was also treated with digitalis, salyrgan, oxygen and other methods. At the time of his admission to the veterans hospital as an acute emergency, he was apparently so ill, that while beriberi was entertained as an admission diagnosis, it was presumably safer to employ all available measures to combat his acute heart failure. We believe that thiamin and strict bed rest were the most important factors in his dramatic response. Garland and McKenney²³ in a study of the roentgen diagnosis of vitamin deficiency cardiac conditions, have emphasized the return of heart size toward normal on thiamin therapy as a diagnostic feature of the disease, and failure of such a response as an exclusion of the diagnosis except in cases of terminal, irreversible failure. Walker²⁴ in a discussion of reversible cardiac enlargement mentions three conditions in which this phenomenon is usually seen, namely arteriovenous aneurysm, myxedema and beriberi. There was no evidence for the first two in our case.

This patient's second attack of acute decompensation is a little more difficult to explain. He had made what was apparently a complete recovery and was sent home on furlough with an ample supply of vitamins which he states he took religiously until a few days before onset of his symptoms of heart failure. He also claims that his diet was adequate. However, it was apparent on careful questioning that his activity was not sufficiently limited and that the factor of physical exertion was apparently the most important in this second episode. It can be seen that his response the second time was prompt, but this time by no means complete. While his edema disappeared and his heart size diminished (figure 2) the latter has still failed to reach normal limits even after five months of continuous hospitalization and intensive therapy. This observation is also in keeping with the general impression that repeated episodes of failure and chronicity of the disease make therapeutic responses much slower and in some cases even entirely absent. This is no doubt due to irreversible myocardial damage and is compatible with autopsy material showing extensive myocardial fibrosis in advanced cases of beriberi.

When this patient was transferred to the Percy Jones General Hospital while convalescing from his second attack of acute failure, he presented a picture of myocardial insufficiency in no way different from many other types of heart disease in the stage of advanced myocardial damage. Only careful neurological examination revealed the remnants of his peripheral neuritis and his tongue still showed some slight redness and papillary atrophy of the tip and edges. Otherwise his state of nutrition appeared excellent. His myocardial reserve was, however, extremely limited and electrocardiographic and roentgenographic studies revealed respectively myocardial damage and a heart still somewhat enlarged. Nor was this picture significantly altered by massive doses of vitamins parenterally and orally although subjectively he felt better than at any time since his internment in Japan and at rest he re-

mained well compensated. An interesting observation was the failure of oral vitamin therapy to maintain this maximum compensation and the recurrence of soreness and atrophy of the tongue when parenteral therapy was discontinued. We interpreted his hypochlorhydria to be on the basis of his previous pellagra.²⁵ In view of his hypochlorhydria and on the basis of some reports of B deficiency occurring in cases of achlorhydria and marked hypochlorhydria,²⁶ dilute hydrochloric acid was given with his meals. This relieved his symptoms and with this addition he seemed to do as well as on parenteral vitamin therapy.

It can thus be seen from this case that there is justification for the broadening of the diagnostic criteria and clinical concept of thiamin deficiency cardiovascular disease. The historically unprecedented circumstances of the past global war have produced some cases of combined "oriental" and "occidental" beriberi and have enabled us to follow patients through their entire course of the disease, illustrating and confirming many of the experimental and clinical observations to date. We have been informed by our patients that several of their prisoner comrades, now out of the army, with whom they have been corresponding, have had relapses with cardiac symptoms, and have turned in to various veteran and army hospitals for further treatment. This fact again emphasizes the need for prolonged care and observation in this disease.

The case of our second patient, now recovering from orthopedic operative repair of his tibia and in good general health, illustrates an instance of the practically complete reversibility possible in even the most severe and prolonged thiamin deficiency under the most propitious circumstances for maximal cardiac involvement. With no evidence of any heart disease now, one wonders whether even the important and frequently emphasized factor of prolonged and strict rest is enough to explain such a contrast in course from that of the first case. Indeed, until the still unknown exact pathogenesis of the lesions of thiamin deficiency are better understood, the syndrome of beriberi heart will remain a perplexing and challenging diagnostic and therapeutic problem.

SUMMARY

1. The development of the modern clinical concept of beriberi cardiovascular disease has been reviewed to show the broadening diagnostic criteria of the disease.

2. Two cases of beriberi cardiovascular disease occurring in American prisoners-of-war in Japan are presented and discussed to show their contrasting clinical course and the possible factors contributing to the variability of the clinical picture.

3. The cases presented tend to confirm the importance of prolonged care, observation, intensive therapy, and enforced rest in cases of beriberi heart disease.

4. We are in agreement with the many modern authors who emphasize that beriberi heart disease need not show classical symptoms in its advanced stages and that the late picture may be very similar to other types of specific and non-specific myocardial insufficiency, the history of dietary deficiency being of paramount importance in the diagnosis.

ADDENDUM

Since the writing of this article the course of case 1 has been followed to his termination on October 30, 1947. The patient did relatively well during the summer of 1947 and was able to engage in limited activity at a convalescent hospital. He remained on a well-balanced diet with oral B-Complex supplements. He was reexamined in September, 1947 at Percy Jones General Hospital. At this time he still showed a prolonged tachycardia on mild exertion, moderate generalized cardiac enlargement and an unchanged electrocardiogram showing low voltage. He was again sent home on terminal furlough. On October 14 he was admitted once again as an emergency to the Veterans' Hospital at Fargo, N. D. with a one week history of shortness of breath, nausea and vomiting. He was found to be in acute cardiac failure with marked cardiac enlargement and an electrocardiogram showing low voltage. He was digitalized and placed on "high vitamin therapy" and seemed to improve during the first week but finally lapsed into progressive failure and died on the sixteenth hospital day. Post-mortem examination revealed marked chronic passive congestion of all the viscera. The heart was greatly enlarged and weighed 470 grams. There was considerable hypertrophy with marked dilation of the entire heart. The consistency of the heart muscle was very flabby, with marked loss of resiliency. The valves and endocardium were normal, as were the coronary arteries. Microscopic sections showed extensive cloudy swelling, loss of striation, fragmentation and fatty degeneration of the myocardial fibers with replacement fibrosis. There were marked interstitial edema and nuclear degenerative changes evident, with small lymphocyte and leukocyte infiltration present. Blood vessels were dilated and filled with red cells. The pathologist's impression was: "Subacute myocarditis of unknown etiology." We believe these changes are consistent with the irreversible damage of chronic beriberi heart.

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MYOCARDITIS IN INSTANCES OF PNEUMONIA *

By OTTO SAPHIR, M.D., and GEORGE D. AMROMIN, M.D., *Chicago, Illinois*

THE occurrence of myocarditis in infectious diseases, and its association with pneumonia, is well known.¹ Recent studies have emphasized the electrocardiographic and clinical aspects of myocarditis in pneumonia, but have not dealt with its histologic aspects. In view of our altered concept of the incidence of myocarditis in other diseases, a detailed histologic study of the myocardium in instances of pneumonia is indicated.

In the following report a study is presented of hearts taken from 67 patients with pneumonia in whom the pneumonia involved at least the total of one lobe. Thus, instances of terminal bronchopneumonia or minimal pneumonia were excluded. Also excluded were infants who lived less than a week. Instances of rheumatic, tuberculous, or of any other specific myocarditis which might have been associated with pneumonia were also excluded, as were the various bacterial and subacute bacterial endocarditides.

In spite of the fact that for years the question as to whether or not to give digitalis to patients with pneumonia was uppermost in the minds of clinicians, it is remarkable how few extensive histologic studies of the myocardium are on record. Stone's² studies are usually quoted. But they do not give any detailed microscopic findings. Neuhoff,³ Liebmann,⁴ Berry,⁵ Roesler and Soloff,⁶ Swift and Smith,⁷ and Spühler⁸ reported only isolated instances.

In this study 67 hearts were examined. Most commonly, four blocks were taken from the left ventricle, four from the right and two to four from the interventricular septum. Several sections were cut from each block and stained with hematoxylin and eosin. In instances of unexpected death, many more sections were cut from the myocardium.

Twenty-six (38.8 per cent) of the hearts disclosed myocarditis. Twelve of these had grossly discernible changes. These were: dilatation of one or both ventricles, flabbiness of the myocardium, hemorrhages in the myocardium, a tigroid appearance of the myocardium and petechial hemorrhages of the pericardium.

Microscopically, inflammatory cells could be recognized in every instance. The type of exudate and the extent of the inflammation varied much. Acute myocarditis was diagnosed 15 times. Neutrophilic polymorphonuclear leukocytes were abundant, but also lymphocytes and endothelial leukocytes of various types were found throughout. The exudate was present mainly in the interstitial tissues, and not infrequently was perivascular. The muscle fibers disclosed severe degenerative changes.

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From the Department of Pathology, Michael Reese Hospital, Chicago, Illinois.

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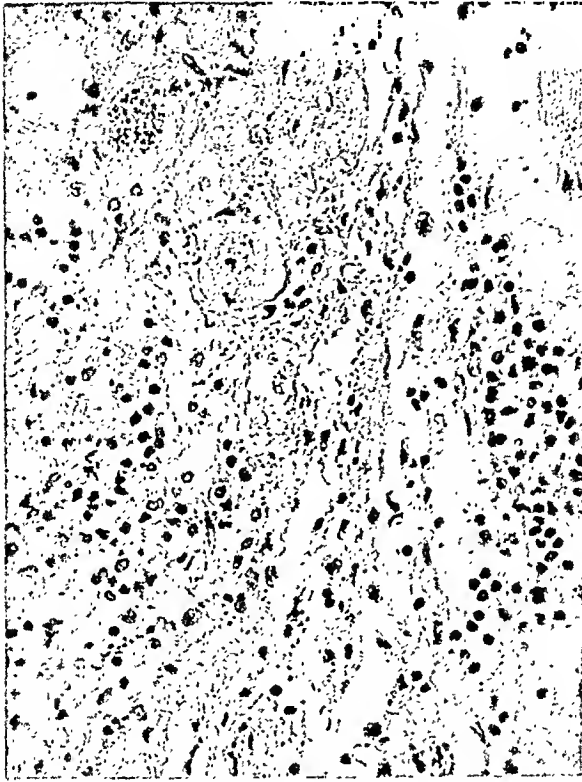


FIG. 1. Note the presence of lymphocytes and polymorphonuclear leukocytes in the interstitial spaces of the myocardium. (Hematoxylin-eosin preparation, $\times 290$.)

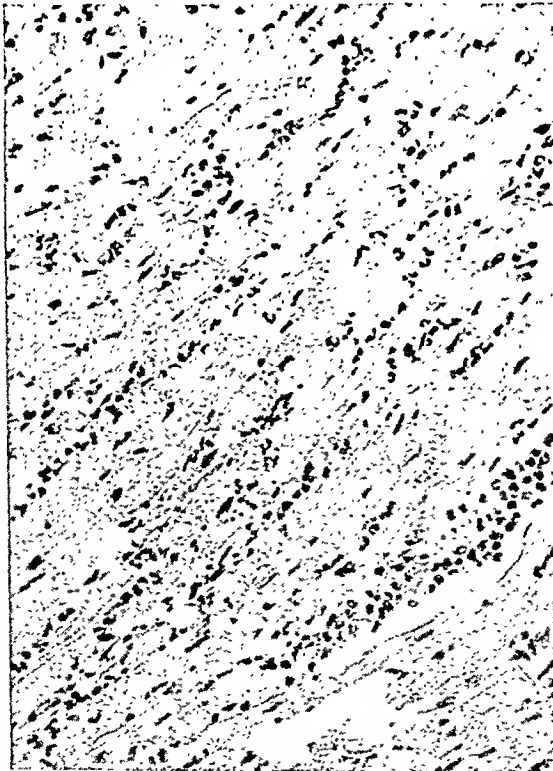


FIG. 2. Note the presence of polymorphonuclear leukocytes and the degenerative changes in the myocardium. (Hematoxylin-eosin preparation, $\times 220$.)

In three instances the myocarditis was classified as acute serous type. Here the exudate was mainly serous, i.e., an edema-like material was present in the interstitial tissue spaces. Small numbers of inflammatory cells were also found, most of which were neutrophils. Cloudy swelling of the muscle fibers was severe.

In eight instances the majority of the inflammatory cells were lymphocytes and endothelial leukocytes. Many of the latter were of the type variously called the Aschoff cell, Anitschkow cell, cardiac histiocyte, etc. It was the type of cell which forms the predominating part of the Aschoff body. Needless to emphasize, in not a single instance were there found structures resembling Aschoff bodies. In addition to these cells, a few polymorphonuclear leukocytes were also noted. Degenerative changes of muscle fibers were also present, but were not as conspicuous as in the acute and acute serous types. Because of the preponderance of lymphocytes and endothelial leukocytes, this myocarditis was termed subacute myocarditis.

Microscopic degenerative changes in the absence of inflammation were encountered in 15 instances. Both cloudy swelling and fatty degeneration were present. These changes were obviously diffuse and seen in any section examined. Sometimes an edema-like material could be made out within the interstitial tissue and a number of blood vessels were seen crowded with polymorphonuclear leukocytes. These changes were classed as degenerative, though they very well may constitute early inflammation.

In summary: Of 67 patients with bronchopneumonia involving a total of one lobe, 26 had myocarditis, either acute, acute serous, or subacute. The hearts of 15 were the seat of degenerative changes.

As mentioned before, only those instances of pneumonia were used in this study where the pneumonic process involved at least the sum total of one lobe. Twenty-two of the 26 patients who had myocarditis had non-specific bronchopneumonia. Seven of these were confluent in type. Unfortunately, the results of the bacteriologic examination were available only in nine instances. Of these, five disclosed non-hemolytic streptococci, two, *Staphylococcus aureus*, and one, each, *Staphylococcus albus* and hemolytic streptococcus respectively. The lungs of three of these 22 patients were also the seat of diffuse bronchiectasis. Sixteen of the 22 instances of bronchopneumonia were recent pneumonias, and in only four evidence of organization of the exudate was found histologically. Two were lipid pneumonias and two others were principally interstitial in type, though the alveoli were also involved. Abscesses were found in three lungs. One of these was also the seat of lipid pneumonia.

After the histologic examination had been completed, the clinical records of the respective patients were studied. Myocarditis was found in eight children with pneumonia. Five of these were under one year; one was 22 months, and one three years old. Five patients were between 61 and 70, and three between 81 and 90 years old. Trying to evaluate clinical evidence of acute heart failure in these patients, the following criteria were looked for:

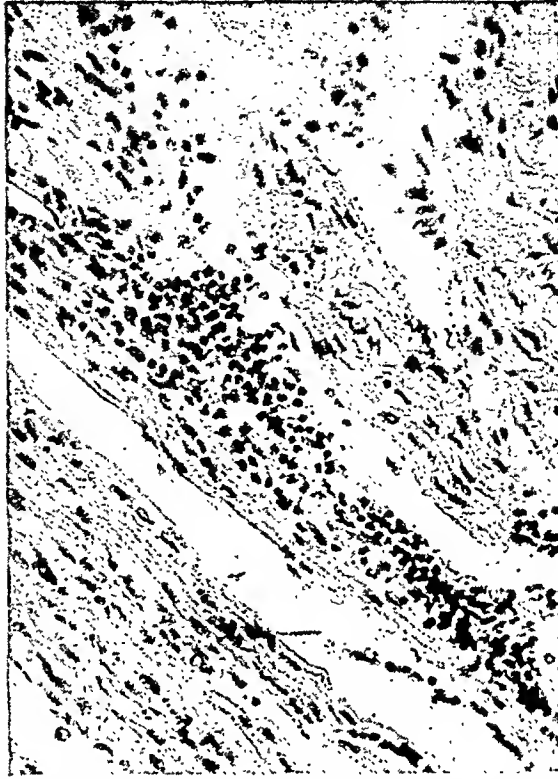


FIG. 3. Note the focal accumulations of many lymphocytes in the interstitial tissue of the myocardium. (Hematoxylin-eosin preparation, $\times 220$.)

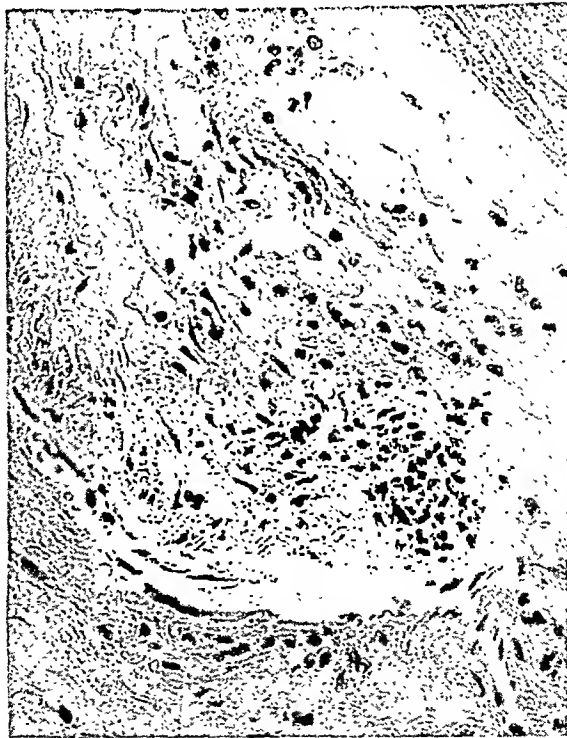


FIG. 4. Note the perivascular infiltrations of lymphocytes and endothelial leukocytes. (Hematoxylin-eosin preparation, $\times 290$.)

discrepancy between pulse rate and temperatures, fall of the arterial blood pressure, dyspnea out of proportion to the involvement of the lung, and unexpected death. Electrocardiographic tracings had been taken in six of these patients.

Discrepancies between the pulse rate and the temperatures were found in 16 patients. In four of the children, the pulse rate was not obtainable. In 10 of our 18 adult patients, a fall of the arterial blood pressure was evident in successive blood pressure recordings. Most commonly, both the systolic and diastolic pressures were reduced.

Dyspnea was very severe in six patients. It is of course difficult to evaluate the myocarditis as cause of the dyspnea, since all these patients had pneumonia. However, from the clinical records it seems that the dyspnea was more pronounced and more persistent than usual in instances of uncomplicated pneumonia as encountered in this study.

Electrocardiographic tracings were taken of eight patients. In two, the electrocardiogram was normal. The respective reports were: (1) Definitely abnormal curve; tendency to low voltage; repeat to rule out anterior wall infarction. (2) Fine auricular fibrillation with A-V block; left ventricular preponderance. (3) Transitory coronary insufficiency. (4) Sinus tachycardia with wandering pacemaker, low voltage, combined heart strain. (5) Sinus tachycardia, ventricular premature systoles, rapid auricular fibrillation later in course.

In the eighth case, the electrocardiogram (figure 5) disclosed auricular fibrillation. At autopsy, hemorrhages and groups of inflammatory cells were seen within the myocardium of the left ventricle and the septum infiltrating and splitting the Bundle of His.

Edema of the lower extremities was present in seven instances. An excess of fluid in serous cavities, excepting the pleural cavities, was found in nine instances; in four of these nine, there was also edema of the lower extremities.

There was no relationship between the severity and extent of the pneumonia, and the degree of myocardial changes. Many of the patients who showed either no myocardial change or only parenchymatous degeneration, had moderate to severe old, organizing as well as acute bronchopneumonia. Approximately the same degree of severity of bronchopneumonia was found in the patients with myocarditides. However, it should be pointed out that most of the myocarditides were associated with recent pneumonias. In instances of older and organizing pneumonia, myocarditis was encountered less frequently. It seems that myocardial involvement in patients with pneumonia occurs relatively early in the course of the disease, or occurs in those instances where there is a recent spread of the disease.

Exactly half of the patients died suddenly. It has been pointed out a number of times that patients with myocarditis often die unexpectedly.¹ In retrospect, it may be stressed that not only was the myocarditis a compli-

cation of the disease, but also was the cause of the unexpected death of 13 patients.

It is well known that experimentally the administration of sulfa drugs may cause myocarditis. Such myocarditides have been found in patients, also. Among our 26 patients with myocarditis, sulfathiazole, sulfadiazine,

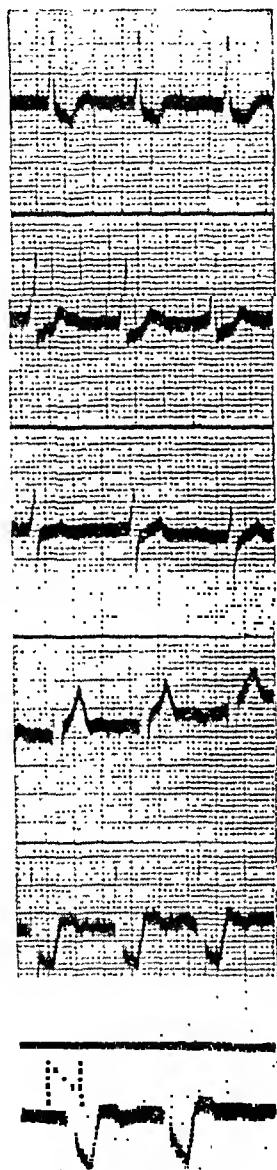


FIG. 5. Average cardiac rate 104/min. The ventricular rate is fairly regular. No P-waves are seen. QRS is up in I_1 and I_2 , diphasic with an S-wave in I_3 . S-T₁ and ₂ are depressed. T₁ is inverted. T₂ is diphasic. S-T is depressed in CF₁ and ₂. T is inverted in CF₃. The mechanism is fine auricular fibrillation. There is left ventricular preponderance. The S-T-T configuration suggests digitalis effect.

sulfasuxidine and sulfamerazine respectively had been given to fourteen. Although it is stated that myocarditis resulting from the administration of sulfa drugs is morphologically somewhat different from myocarditis found in acute infectious diseases, our experience indicates that such a differentiation is very difficult to make. The number of eosinophilic cells and monocytes is found to be only slightly larger in the former than in the latter.

However, it seems more significant that morphologically the myocarditis in the 14 patients who received sulfa drugs did not vary in essentials from that of the 12 patients who received no sulfa medication.

Very recently Thomson et al.⁹ studied electrocardiograms made during and after pneumococcus pneumonia. Thirty-five of their 92 patients exhibited electrocardiographic alterations. Ten of these patients died. Autopsies were performed in five of those who had disclosed electrocardiographic changes. Except for acute fibrinous pericarditis in one, no significant gross or microscopic evidence of heart disease was found. It is noteworthy that these authors state that the appearance of the T-wave changes raise the question of whether or not they represent evidence of myocarditis; but none was found. This is interesting in the light of our findings of myocarditis in 38.8 per cent of our pneumonia patients. Unfortunately, Thomson et al. do not state whether routine sections were taken from the myocardium or whether a number of blocks of the myocardium were examined. From our experience, it is obvious that a few sections of the myocardium, taken at random, do not necessarily represent its true state. From this and previous studies, we have learned that to establish the presence of myocarditis, many sections must often be examined. Even though a few do not disclose the presence of inflammatory changes, the heart may still harbor myocarditis. In our opinion, myocarditis is often found if an attempt is made to rule it out. This can be done only by the examination of relatively many sections. This is particularly so since myocarditis in instances of pneumonia is ordinarily spotty, rarely diffuse.

As has been shown before, the histologic changes in the heart in instances of pneumonia have not received much attention, and most of the opinions as to the state of the myocardium are based on either gross study of the heart or on the examination of a few histologic sections. This is particularly so in Stone's² study which is always quoted relevant to the discussion of this problem. And yet there is an extensive older literature on the evaluation of cardiac stimulants in instances of pneumonia. It seems that the older clinicians were impressed with some evidence, at least, of myocardial failure. Also some of the electrocardiographic changes as mentioned in the literature could be interpreted as myocarditis as Thomson et al.⁹ stated. It is perhaps because the pathologists have failed to find myocarditis in the few routine sections usually cut from the myocardium, that the clinicians have come to mistrust their ability to recognize it clinically.

SUMMARY

The hearts of 67 patients with bronchopneumonia, involving at least one lobe of the lungs, were studied by multiple microscopic sections. Twenty-six, or 38.8 per cent of these revealed inflammatory changes sufficient to warrant the term "myocarditis." Fifteen were classified as acute myocarditis, three as acute serous, and eight as subacute myocarditis. The out-

standing clinical criteria pointing to the diagnosis were found to be: Disproportion between the pulse rate and the temperature, drop in the arterial blood pressure, cyanosis out of proportion to the apparent pulmonary involvement and, unexpected death. Six of these 26 patients exhibited electrocardiographic abnormalities. Emphasis was placed upon the necessity of examining multiple sections of the myocardium either to establish or to disprove a diagnosis of myocarditis.

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THE RÔLE OF HORMONES IN THE TREATMENT OF OBESITY *

By M. M. KUNDE, Ph.D., M.D., *Chicago, Illinois*

OBESITY due to specific endocrine disturbances is described in practically every textbook on endocrinology.¹ A résumé of this literature indicates that hypofunction of the pituitary heads the list of all endocrine disorders responsible, either directly or indirectly, for excessive deposition of adipose tissue. Hypopituitary adiposity is described as girdle type of obesity. Next in order of frequency is the hypogonad type with excessive trochanteric fat deposit. Other types are: adiposogenital pituitary (hypogonad-hypopituitary) with enormous girdle fat deposits and comparatively slender terminal extremities; familial obesity, a term applied to overweight siblings otherwise normal; pancreatogenic type due to faulty function of the Islands of Langerhans; the orthopedic type in which obesity follows deformities limiting normal exercise; the juvenile or Fröhlich syndrome type; the Cushing syndrome, or pituitary basophilism; and hyperadrenocorticism² with plethoric obesity confined to the face, neck, chest and abdomen (buffalo type).

The advocacy of hormonal products, claimed to be specific or helpful in weight reduction of these various types of obesity, has created a state of confusion difficult to parallel in modern therapeutics.

In opposition to the advocates of the endocrine treatment of obesity there exists a group of investigators³ who assert obesity to be a problem merely of discrepancy between energy exchange of the individual. They base the solution of the problem on a carefully calculated diet, the caloric value of which equals the energy expended by the individual as estimated from the basal metabolism, age, exercise and general activity. These investigators place little emphasis on the endocrine phase of the problem of overweight, and grant no consideration to the possibility of unknown constitutional metabolic conditions which may not conform to the known law of energy exchange in man.

This report is based on the study of a group of patients with obesity, totaling 50 in number and varying in age from 34 months to 55 years. All had been referred for endocrine treatment either because of debilitating overweight, presumably due to some vague endocrinopathy, or because of some specific endocrine dysfunction with which the overweight was associated. Some of these were treated for obesity for the first time. Others had previously attempted to reduce on a carefully calculated low caloric diet and could not adjust to such a regime. A small number had previously taken hormone

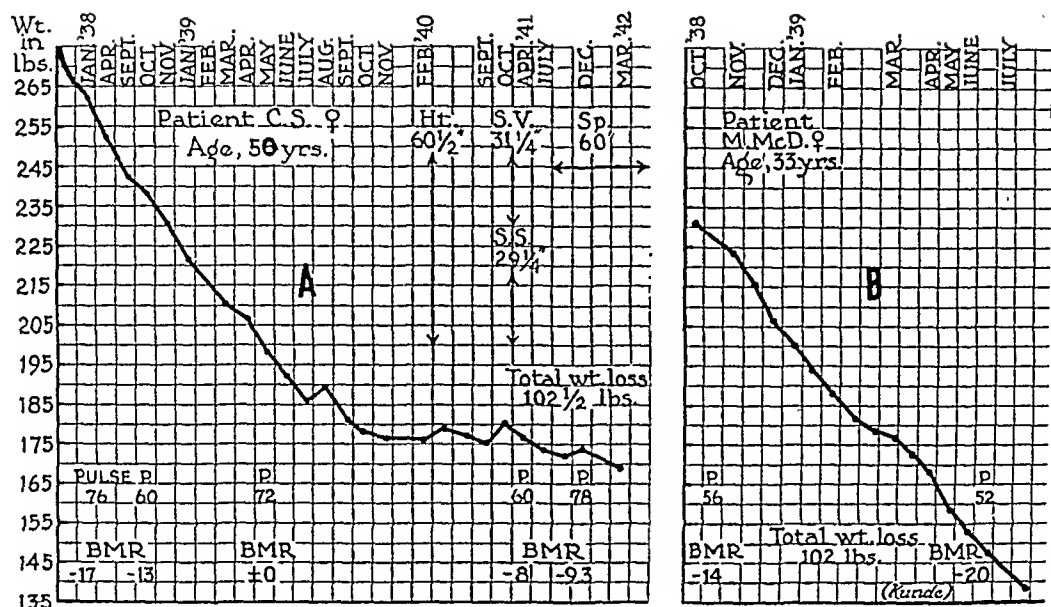
* Read before the Association for the Study of Internal Secretions at San Francisco, California, June 28, 1946.

From Northwestern University Medical School and Outpatient Endocrine Clinic of Cook County Hospital and Chicago Maternity Center.

CHART I—Continued

Case and Age	Date	Weight in Lbs.	Sella-Turcica	B.M.R.	Cholesterol*	Ca*	Phos.*	Glucose Tolerance*	Blood Pressure	Loss Lbs.
H. D. —K 27 yrs.	10-28-39 2-9-42	215 190	12 mm.	— 3	133	9.1		90; 166; 125; 100; 67	118/70	25
B. Ba —K 44 yrs.	7-5-39 8-25-39	173 160½	History: Menarche—12 yrs. 28 day regular normal cycle. No pregnancies. small	+ 9	159	9		76; 125; 143; 125; 83	90/70	12½
E. E. 39 yrs.	2-26-40 5-6-41	254 242	History: Periods normal to date. 1 pregnancy. —20					89; 142; 166; 182; 77	140/70	12
E. O. —K 14 yrs.	11-29-44 6-10-46	178½ 128	History: Normal cycles to date. 9 years ago patient had much thyroid medication. History: Menarche—11 yrs. Normal regular cycles to date. Infantile paralysis in 1939 with resultant impairment in motion of both legs.						120/70	50½
J. B. —K M 17 yrs.	6-25-45 9-4-45	283½ 258	normal	—12	152	11.6		88.2; 118; 102; 98; 89	138/70	25¾
G. B. —K 25 yrs.	6-25-45 9-4-45	237 217	History: Normal male with marked obesity but normal genital development. normal		164	11		95; 142; 108; 98; 91	132/90	20
S. S. 41 yrs.	7-15-41 3-23-42	283½ 217	History: Normal menstrual history. + 5 — 9		294 278	9.4	3.2	92; 151; 188; 163; 111 52; 126; 140; 121; 121	186/85 125/80	66½
E. D. —CCH 35 yrs.	10-5-45 6-7-46	175 135	History: Menarche—12 yrs. Regular normal cycles to date.							40
C. D. —K 17 yrs.	4-16-44 6-13-44	175½ 155½	History: Normal menstrual periods to date. —12					80; 95; 94; 80		20
E. B. —K 36 yrs.	9-13-43 12-14-43	167 134	History: Menarche—13 yrs. Normal regular periods. +14							33
Z. W. —K 36 yrs.	2-13-39 7-20-39	262½ 198	History: Menarche—14 yrs. Regular to date. normal + 7		192	10		86; 121; 118; 85 83; 133; 117; 83; 66	140/90	64½

* Mg. per 100 c.c. blood.



GRAPH 1 A. Charts progressive weight loss in patient C. S. over more than 4 yrs. Also, measurements in inches of height (Ht.); span (Sp.); symphysis to vertex (SV); symphysis to soles (SS). Patient lost 102 lbs. in weight. B. Charts progressive weight loss of 102 lbs. in patient M. McD.

products with failure to lose weight. The group is thus heterogeneous, consisting of some patients treated for obesity for the first time, and others re-treated after endocrine therapy and carefully calculated low caloric diets had failed.

As previously mentioned some of these obese patients presented history or signs or symptoms of specific glandular dysfunction which had been tentatively diagnosed in the general medical clinic. This diagnosis was definitely established, or ruled out, in the endocrine clinic by special laboratory investigations, special physical examinations, and more detailed history. These specific endocrinopathies were mostly hypofunction of the gonads (chart 3), and as they did not seem to impair the health or well being of the patient at the time, they were disregarded. No patient with diabetes or marked hypothyroidism was included in this study. Weight reduction in these patients was handled as any other major medical problem and the patient reported to the physician at each clinic visit.

FIG. 1 A. Obesity in early middle age. Patient, M. D., age 33 yrs. Initial weight, 231 lbs. No significant findings excepting overweight. See chart 1 for laboratory data, and history. Clinical diagnosis, hypopituitary obesity. B. Same patient after weight loss of 102 lbs. See graph 1 B for progressive weight loss over 10 months.

FIG. 2 A. Obesity in late middle age. Patient, C. S., age 50 yrs. Clinical diagnosis, hypopituitary obesity. B. Same patient after loss of 102 lbs. See chart 1 for laboratory data and history, and graph 1 A for progression of weight loss and variations of weight during maintenance of reduced weight.

FIG. 3. Obesity in post-menopausal state. Patient, H. St., age 45 yrs. See chart 2 for laboratory findings and history. Clinical diagnosis, endocrine obesity. Loss of 64 lbs. in weight in eight months.

FIG. 4. Obesity with hypo-ovarianism. Patient, D. N., age 23 yrs. Menarche at 16 yrs.; only two or three menstrual periods per year (scant flow). Lost 56 lbs. in one year. See chart 3 for laboratory findings.

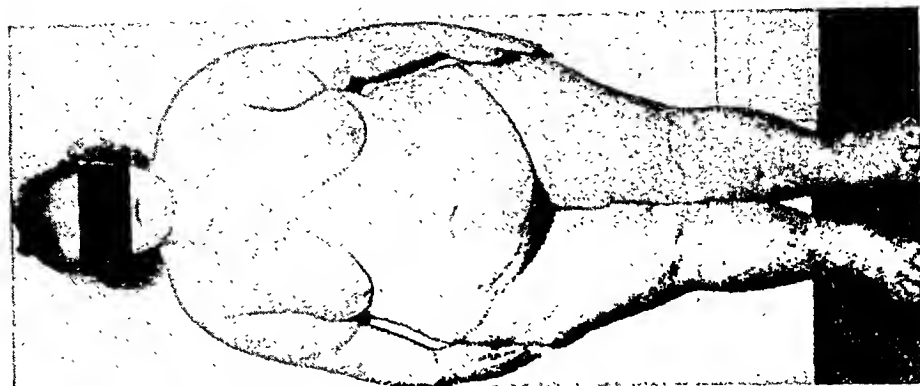


Fig. 4.



Fig. 3.



Fig. 2.

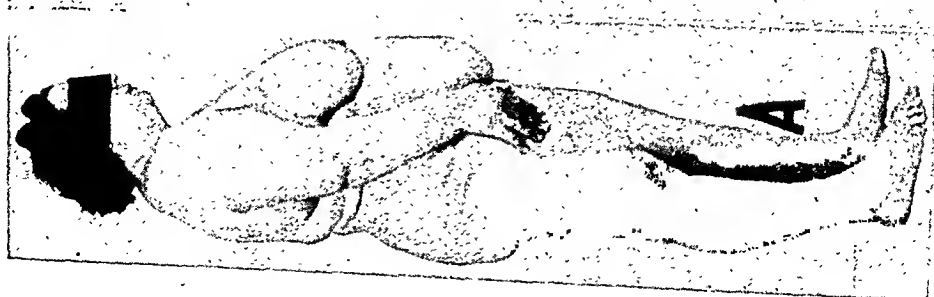


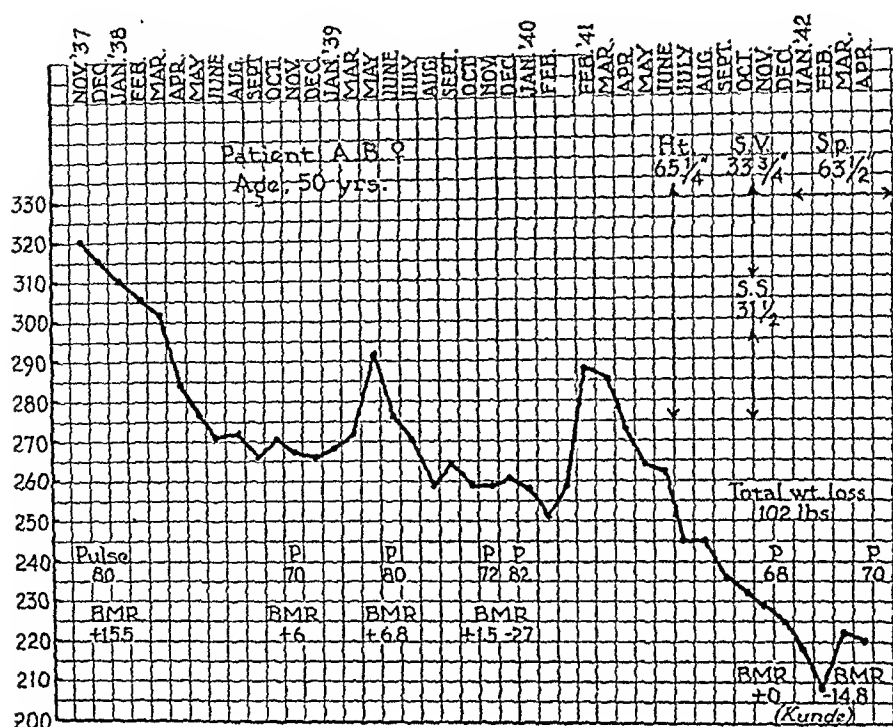
Fig. 1.

CHART II

Obesity in Patients in the Climacteric or Post-Menopausal State with No Ovarian Dysfunction during Childbearing Years

Case and Age	Date	Weight in Lbs.	Sella-Turcica	B.M.R.	Cholesterol*	Ca*	Phos.*	Glucose Tolerance*	Blood Pressure	Loss Lbs.
A. B. 50 yrs.	11-30-37 2-10-42	320 218	14 mm.	+ 6 -14.8	295 333	9.9 10.4	3.4 3.7	101; 159; 137; 112; 114 83; 142; 127; 135; 119	130/80 132/84	102
	History: Menarche—14 yrs. Regular normal 28 day cycles. 1 pregnancy. Completion of menopause 2 yrs. before beginning weight reduction.									
B. J. U. 51 yrs.	5-23-38 1-17-39	207½ 180	normal	+ 9	.260				138/76	27½
	History: Menarche—12 yrs. Normal regular 28 day cycles. 7 pregnancies. Menopause at 50 yrs.									
E. Er. 55 yrs.	4-3-40 11-17-41	201½ 142	12 mm.	+ 9 - 5	220 203	9.7	3.76	126; 198; 258; 246; 152 93; 125; 185; 245; 175	192/112 140/80	68½
	History: Menarche—13½ yrs. Normal regular cycles. Menopause at 52 yrs. 2 pregnancies. Marked hypertrichosis of face.									
M. L. 55 yrs.	4-8-40 3-20-41	256 197	12 mm.	+ 2.3 -15	332 272	9.8 10.4	3.7 3.9	110; 182; 168; 136 107; 162; 183; 111	148/85	59
	History: Menarche—15 yrs. Cycles normal. Marked hirsutism of face which has increased since menopause. Menopause 8 years ago.									
L. A. 54 yrs.	4-27-40 4-14-42	316 246		+ 4	384	10.1		131; 238; 294; 282; 147		70
	History: Menarche—12 yrs. Regular periods. 1 pregnancy. Menopause at 52 yrs.									
H. St. 45 yrs.	11-11-41 7-10-42	244 180		+ 5.6	296	10.1	3.2	165; 131; 361; 325; 220		64
	History: Menarche—12 yrs. Normal regular cycles. Menopause at 42 yrs.									

* Mg. per 100 c.c. blood.



GRAPH 2. Charts weight loss in patient A. B. over a period of 4 yrs. and 4 mos. This patient belongs to the post-menopausal group. Body measurements are also indicated.

Procedure of Treatment. Before the initiation of treatment for obesity, the patient undergoes the physical examination necessary in special endocrine cases, and a careful medical history with special reference to inherent and acquired endocrine disturbance is taken. Laboratory tests made at the beginning (and whenever possible, at the end of the period of weight loss) include basal metabolism, glucose tolerance, urine analysis, complete blood count, blood cholesterol, and blood calcium and phosphorus. Roentgen-rays of the sella turcica and epiphyses are requested whenever other findings suggest that these might be helpful or essential.

Hormonal products are definitely not prescribed or used during the entire period of weight reduction. No calculated caloric diet is suggested; consequently the services and advice of dietitians need not be employed. But much emphasis is placed upon the need for reëducation of the appetite. These overweight patients are informed that there are no known hormones that can cure the obesity, but that their adiposity can be satisfactorily reduced by strictly adhering to a prescribed dietary. They are warned that if the previous faulty food habits are again indulged in, increase in weight will recur.

A list of food substances chosen to constitute a high protein, low fat, low carbohydrate diet, with no calculation of caloric values is then prescribed. It includes lean meat, fish and fowl in large portions (approximately double or more the amount of a normal serving) at least twice daily. (All possible fat is scrupulously removed from the meat, and no fat as such, either animal

CHART III
Obesity in Patients with Hypo-ovarian Function

Case and Age	Date	Weight in Lbs.	Sella-Turcica	B.M.R.	Cholesterol*	Ca*	Phos.*	Glucose Tolerance*	Blood Pressure	Loss Lbs.
E. R. 30 yrs.	9-3-40 3-10-42 History: Menarche—13 yrs. Cycles varied two or more months until 18 yrs. Married at 18. Cycles regular since then. No contraceptives used. No pregnancies. Striae on arms and thighs. Masculine escutcheon. Hirsutism marked between breasts and lateral aspect of thighs; circumoral beardiness of 10 yrs. duration.	195½ 150	15 mm.	+10.6	246	9.6	3.74	84; 134; 154; 125; 110	138/90	45½
P. B. 43 yrs.	10-29-40 2-17-42 History: Menarche—12 yrs. Cycles 1 to 6 mos. up to age 22. Since then 1 to 2 mos. apart. Gained 50 lbs. during 31st yr. 4 pregnancies.	225½ 175		+ 4.7	254	10	3.09	91; 137; 171; 250; 158	112/80	50½
O. D. 27 yrs.	11-13-40 5-27-41 History: Menarche—13 yrs. Regular 28 day type until 18 mos. ago. Since then periods vary from 2½ to 3 mos. and are profuse. Weight approximately 250 lbs. for past 6 yrs. 3 pregnancies.	258½ 207	11 mm.	+ 1.6		9.7		90; 239; 220; 235; 170	140/95	51½
E. P. 34 yrs.	10-11-38 3-7-39 History: Menarche—15 yrs. Variations 1 to 7 mos. Married twice. No pregnancies. No contraceptives. Obesity began at 19 yrs.	226½ 188½	13 mm.	+ 8 + 4	333	10.5	2.25	136; 240; 290; 245; 143	130/80	38
D. N. 23 yrs. —K	3-11-41 3-23-42 History: Menarche—16 yrs. Cycles 3 to 4 mos. apart. 3 day flow; scant. No pregnancies.	253 197		+20 +16		9.5	3.39	106; 182; 137; 134; 121	106/50	56

CHART III—Continued

Case and Age	Date	Weight in Lbs.	Sella-Turcica	B.M.R.	Cholesterol*	Ca*	Phos.*	Glucose Tolerance*	Blood Pressure	Loss Lbs.
B. Jo. 37 yrs.	5-2-39 2-13-40 History: Menarche—14 yrs.	248 186		+13 -3.4	283 200	9.3	3.9	107; 235; 213; 259; 111	246/160 184/124	62
E. Pl. 54 yrs.	4-1-41 4-17-42 History: Never menstruated.	236½ 202	10 mm.	+5 -20	333 301	9.6 9.7	3.1 3.7	122; 213; 236; 167; 90 89; 170; 184; 171; 160	No contraceptives. Could not become pregnant again. Weight at age 27, 125 lbs.	30½
E. D. 31 yrs.	10-10-39 9-10-40 History: Menarche—11 yrs. Normal and regular to age of 19. From 19 to 25 yrs. periods varied from 3 to 8 mos. Periods stopped in 1934 at the age of 36. Marked growth of hair on arms, upper lip, chin and legs. Periods began again Jan. 1940 and have been regular to date with fairly normal flow.	222 179	13 mm.	+13 +7.6	275	10 10.1	2.8 3	138; 94; 225; 230; 132 85; 154; 163; 123; 90	162/110	43
D. M. 21 yrs. —K	8-10-38 7-15-39 History: Menarche—14 yrs. Cycles 35 days apart.	195 133	normal	+1	132	9.9		100; 143; 137; 111	120/70	62
E. S. 16 yrs. —K	2-14-39 4-13-39 History: Menarche—11 yrs. Regular to 14. Since then cycles are 3 to 4 mos. apart and last from 3 to 30 days.	249 226	normal	+4	167	8.9		100; 154; 166; 117; 111	125/60	23
D. A. 14 yrs. —K	10-23-39 5-10-40 History: Menarche—12 yrs. Cycles every 2 to 4 months; scant.	200 156½		-12	182	9			112/70	43½
V. Mc. 39 yrs.	2-2-43 5-16-44 History: Menarche—12 yrs. Irregular up to age of 33, periods varying from 1 to 11 months. Regular from 33 to date.	315 197½		-7.5 -6.5	189 183			182; 242; 238; 223 84; 133; 130; 124; 120	162/90 158/82	117½

* Mg. per 100 c.c. blood.

or vegetable, is added.) Eggs (two daily) are advised, and also uncreamed cottage cheese and gelatin. The vegetables include cabbage, cauliflower, broccoli, brussels sprouts, kraut, spinach, celery, asparagus, string beans, onions, radishes, lettuce and other greens, cucumbers, mushrooms, summer squash, tomatoes, rhubarb, endive, okra, and eggplant. The fruit consists of grapefruit, either canned or fresh, always unsweetened (as no sugar is prescribed), strawberries, and cranberries sweetened with saccharin. Lemon juice and vinegar are also included. Tea, coffee and salt habits are discussed and not interfered with unless there is a special contraindication or unless the amounts used have been excessive. If they are immoderate salt eaters, they are advised that the amount of salt added to the food in the process of preparing the meal is usually quite adequate. To insure against certain mineral and vitamin deficiencies (inasmuch as they are allowed to choose what they desire from the above list and to eat *ad lib.*), calcium, in the form of calcium lactate (30 to 40 grains), vitamin D (600 to 1000 U.S.P. units), and 12 to 15 plain brewer's yeast tablets (7½ grains each) are included as a fixed part of their daily dietary intake.

Results. Data tabulated in chart 1 show results on a group of obese patients ranging in age from 14 to 50 years. Patients of this group have body configurations of the type commonly described as pituitary obesity, in which the overweight has been presumed to be due to hypofunction of the pituitary (figures 1 and 2, and graph 1 A and B). Reduction in body weight in individuals of this group varied from 12 to 102 pounds. The absolute number of pounds lost by each individual depends upon the initial

CHART IV
Obesity in Patients with Surgical Menopause

Case and Age	Date	Weight in Lbs.	B.M.R.	Cholesterol*	Ca*	Phos.*	Glucose Tolerance*	Blood Pressure	Loss Lbs.
M. V. 53 yrs.	7-11-40 3-10-42	201 149½	- 7 - 9	245	9.8	2.7	119; 158; 166; 132; 125	158/105	51½
History: Menarche—15 yrs. Regular periods, scant; vaginal hysterectomy 10 years ago. 4 pregnancies.									
M. H. 36 yrs.	6-24-41 4-7-42	193 148½	-10 - 5	266 240	9.7	2.9	155; 190; 260; 156; 122 120; 172; 195; 137; 122	120/88	44½
History: Menarche—13 yrs. Regular 28 day cycle. 4 pregnancies. Vaginal hysterectomy at 32. Rapid gain in following 18 months.									
L. B. 31 yrs.	1-11-40 5-15-41	156 130						120/72	26
History: Normal cycles until 28. 2 pregnancies. Hysterectomy at 28.									
S. S. 56 yrs.	4-5-41 3-10-42	227 193	+ 3.8 + 8.5		9.7	3.38	105; 120; 172; 98; 59	165/100 160/100	34
History: Menarche—13 yrs. Regular 28 day cycle, 6 to 10 day flow. 2 pregnancies. Both ovaries removed at 32, followed by menopause. Hot flashes for 10 years. Gained 30 lbs. from 1-5-41 to 4-5-41.									
T. M. —K 39 yrs.	2-22-46 5-21-46	177 147					97; 103; 95; 52	102/70	30
History: Complete ovariectomy at age of 19.									

* Mg. per 100 c.c. blood.

CHART V
Obesity in Juvenile Patients

Case and Age	Date	Weight in Lbs.	Sella-Turcica	B.M.R.	Cholesterol*	Ca*	Phos.*	Glucose Tolerance*	Blood Pressure	Loss Lbs.
D. F. —K 11½ yrs.	8-7-37 11-27-37	118½ 101	11 mm.	— 8	136	9		77; 118; 74; 77; 77		17½
B. O'L. —K 13 yrs.	7-25-39 12-21-39	162 126	History: Male.	—15	156.2	10.8	3.4	95.2; 166; 142; 125; 117	Tall. Mentally keen.	
G. O'L. —K 11 yrs.	7-25-39 12-21-39	162 128	History: Female.	No menstruation.	151.5	11.3	3.1	78; 153; 166; 154; 143	Mentally keen.	36
P. B. —K 34 mos.	1-16-43 6-15-43	54 41	History: Male.	Hypogenitalism with girdle type of obesity.				Growth normal. Mentally keen.		34
S. K. —K 11 yrs.	2-12-42 4-18-42	152 135	normal	History: Female.	Height 41½"			Mentally defective.		
L. F. —K 13 yrs.	12-9-39 5-11-40	216½ 186½		History: Female.	Height 65¼"			Mentally normal.	96/70	17
J. S. —K 18 yrs.	7-14-44 3-16-45	238 184	normal	History: Female.	Normal in height.			Mentally normal.		30
	History: Male.	Normal mentally.	Hypogenitalism.	Hyperadrenocorticism with buffalo type of obesity, striae and acne.	11.6			71; 105; 153; 140; 120	192/130 138/108	54

* Mg. per 100 c.c. blood.

body weight and the length of time that the patient continues this dietary regime.

Chart 2 presents data from the records of a group of obese women most commonly found in clinical and office practice, namely the post-menopausal woman who consoles herself with the idea that her continuous gain in weight is due to cessation of ovarian function. Figure 3 is typical of this class with



FIG. 5. Obesity in juvenile patients. Patient, D. F., age 11 yrs. Lost $17\frac{1}{2}$ lbs. in months. Patient, G. O'L., age 11 yrs. Lost 34 lbs. in five months. Patient, B. O'L., 13 yrs. Lost 36 lbs. in five months. Patient, P. B., age 34 months. Lost 13 lbs. in five months. See chart 5 for laboratory data and history.

large apron of fat, pendulous breasts and girdle type of obesity. Weight loss in this group varied from $27\frac{1}{2}$ to 102 pounds (graph 2). The usual diagnosis is menopausal obesity.

Chart 3 embodies the tabulated results of studies on obese women in the child bearing years. In addition to obesity a definite diagnosis of hypofunction of the ovaries had been established. No ovarian stimulating substance



FIG. 6.

FIG. 7.

FIG. 6. Obesity in the physically handicapped Patient, L. H., age 19 yrs. Clinical diagnosis, osteogenesis imperfecta with orthopedic type of obesity. This patient suffered from much restriction of physical activity. Lost $24\frac{1}{2}$ lbs. in weight in $5\frac{1}{2}$ months. See chart 1 for laboratory data and history.

FIG. 7. Obesity in patient B. J., age 38 yrs., who had failed previously to reduce on thyroid therapy. Clinical diagnosis, buffalo type of obesity. See graph 4 A showing results of failure to reduce weight by thyroid therapy, 6 to 8 grains daily. Graph 4 B shows weight loss of 64 lbs. in 16 months on high protein, low fat, low carbohydrate *ad lib.* diet, and no endocrine therapy.

or other hormones were prescribed during the period of weight reduction. Weight loss up to $117\frac{1}{4}$ pounds was recorded. Hypogonad obesity is the usual clinical diagnosis of this type of case (figure 4).

Data on obese patients who had undergone major pelvic surgical operations, followed by cessation of menstruation, are tabulated in chart 4. These patients likewise have been clinically diagnosed as hypogonad obesity, but

are differentiated from the preceding group because of extirpation of ovaries at some previous date which resulted in surgical menopause. The same satisfactory loss in weight on this dietary regime was observed in this group.

Chart 5 presents results obtained on overweight juvenile patients with clinical diagnoses of Fröhlich syndrome type of obesity. Seven patients of this type (three males and four females) were studied. They varied in age from 34 months to 18 years. All received only the high protein, low fat, low carbohydrate *ad lib.* dietary for weight reduction. Weight loss of more than 50 pounds was accomplished on this regime before specific gonad therapy was instituted (figure 5). One outstanding case of hyperadrenocorticism with hypo-genitalism, striae, polycythemia, acne and hypertension was included as this group.

Data on two outstanding cases of the physically handicapped with marked obesity (orthopedic type) are also included. Laboratory data and history of both patients are tabulated in chart 1. The initial weight of one, L. H., age 19 years, (figure 6) was 132½ pounds. The other one of this type, E. O., suffered marked loss in control of both legs after poliomyelitis four years previously. This patient lost 50½ pounds. The results of an outstanding case of familial obesity (V. Mc.) are tabulated in chart 3. Figure 8 shows the patient, V. Mc., with her obese siblings and normal parents. This patient lost 117¼ pounds after having been overweight all her life. Her clinical diagnosis, prior to her transfer to the endocrine clinic, was familial type of obesity.

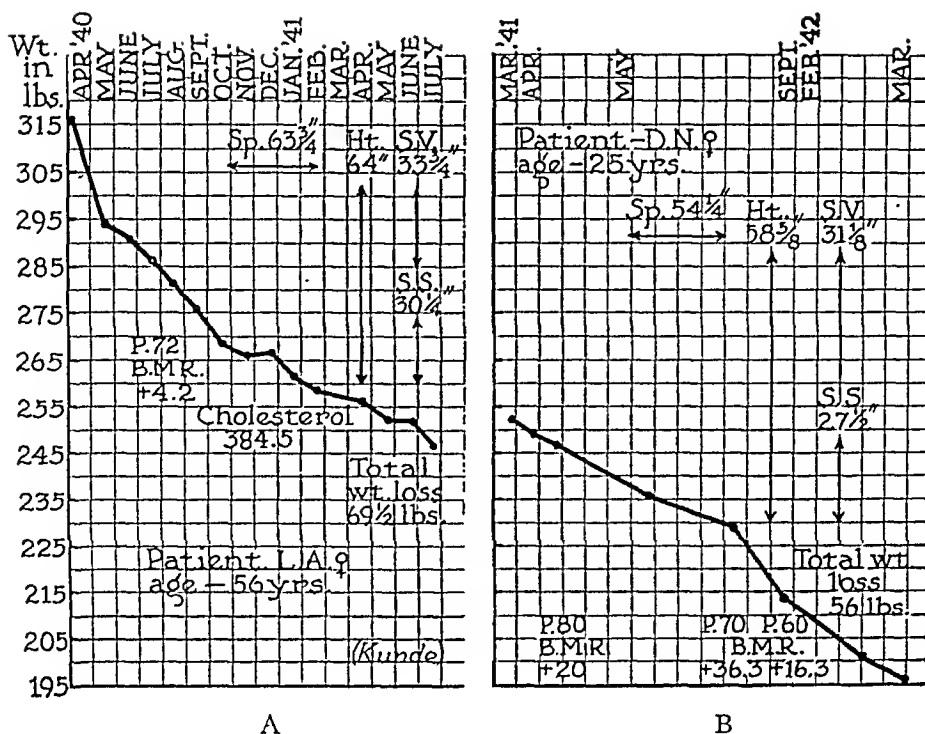
DISCUSSION

A group of 50 overweight patients who had previously been diagnosed as endocrine obesity and who exhibited body configurations corresponding to all types of so-called endocrine obesity, lost weight on a high protein, low fat, low carbohydrate, *ad lib.* dietary, supplemented with minerals and vitamins. No calculation of caloric values was encouraged. A few of these patients had given a history of increased appetite with resultant excessive food intake. But most of them had acquired a taste for carbohydrates and indulged in them in excess of the amount which their body could metabolize without excessive deposition of fat. The fundamental cause of their obesity seems to be due to some unknown constitutional discrepancy in their metabolism. This makes it necessary for them to exist on a dietary containing a greater proportion of protein and less carbohydrate and fat than is required for the individual who does not become excessively obese on the average American dietary. Be that as it may, the fact remains that no endocrine product known to therapeutics at this time is necessary or helpful in reducing the body weight of obese patients.

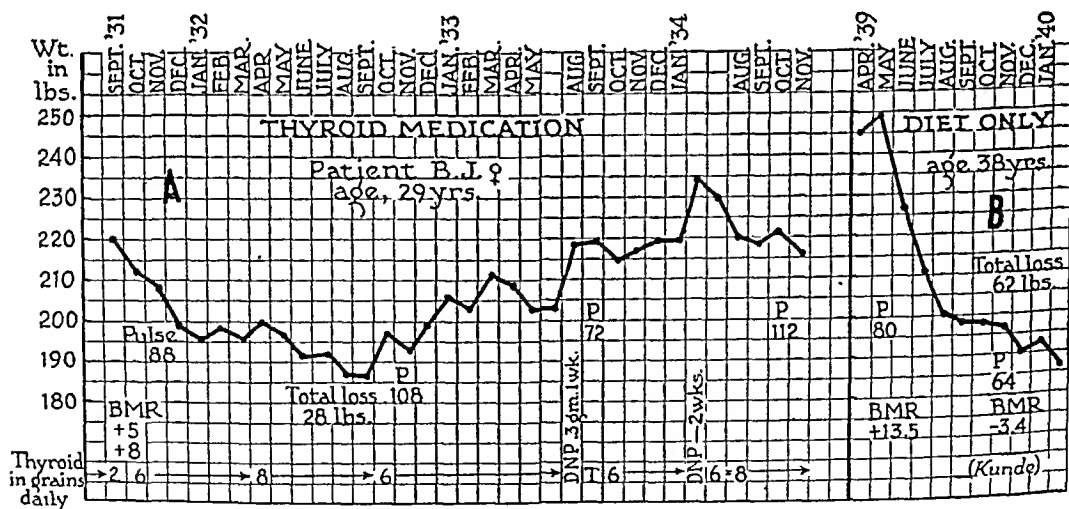
Thyroid hormones should be administered solely for the correction of a specific hypothyroidism. When this is properly accomplished, the obesity will take care of itself or it should be managed by dietary regulation. The use of thyroid extract, in patients with adiposity but with no hypothyroidism,



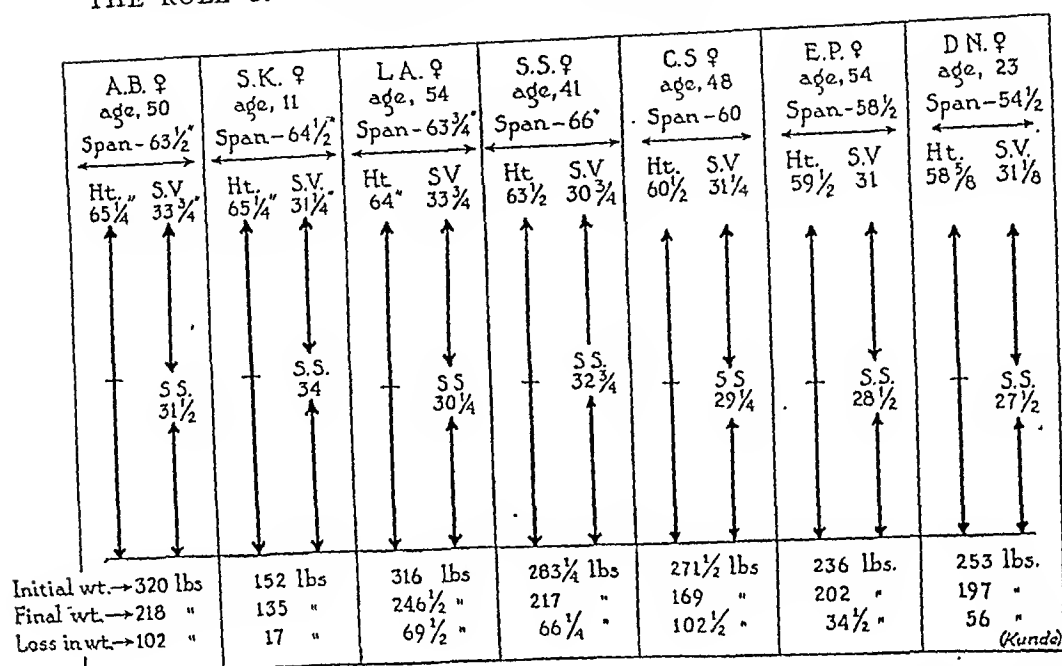
FIG. 8. Obesity of the familial type, showing 3 obese siblings and normal parents. Patient, V. Mc., is first photographed at the age of a few months, a plump baby, and at 3 yrs. of age weighing 106 lbs. Next photo shows V. Mc. at 8 yrs. of age weighing 250 lbs. Again photographed at 15 yrs. weighing 419 lbs. The next photograph was taken at 19 yrs. and the patient weighed 432 lbs. At the age of 39 yrs. the patient weighed 315 lbs. at which time she came to the clinic and was reduced by the method of high protein, low fat, low carbohydrate *ad lib.* diet. On this dietary regime the patient lost $117\frac{1}{4}$ lbs. in $16\frac{1}{2}$ months. See chart 3 for laboratory data and history.



GRAPH 3 A and B. Comparison of weight loss in A, post-menopausal patient, L. A., age 56 yrs., weight loss 69½ lbs., with B, young hypo-ovarian patient, D. N., age 23 yrs., weight loss 56 lbs.



GRAPH 4 A. Comparison of weight loss in same patient, B. J., A with thyroid medication and B with high protein, low fat, low carbohydrate *ad lib.* diet. A shows results in 1931, at age of 29 yrs. patient weighed 220 lbs. Thyroid therapy varying from 2 to 8 grains daily was given from September, 1931 to September, 1932. The patient showed marked signs of thyrotoxicosis before 30 lbs. in weight were lost. Thyroid was then reduced to 6 grains daily for the next 8 months, at the end of which time the patient's weight had increased to its original figure of 220 lbs. despite a daily intake of 6 grains thyroid. Again thyroid, 6 to 8 daily with but few interruptions was given until November, 1934, with no loss in weight. B. In April, 1939, the same patient came back to the clinic weighing 250 lbs. No thyroid or other endocrine products were given, but the patient was placed on the high protein, low fat, low carbohydrate *ad lib.* diet and lost 64 lbs.



GRAPH 5. Obesity with variations in skeletal measurements found in endocrinopathies. Weight loss, in this group on the high protein, low fat, low carbohydrate diet proceeded in the same manner as in those with normal skeletal proportions. Sp. = Span; Ht. = Height; SV = Symphysis to vertex; SS = Symphysis to soles.

solely for the purpose of attempting to effect weight loss by stimulating metabolism, is fraught with disappointment and failure. Such overweight patients soon manifest the symptoms of severe induced hyperthyroidism with little or no weight loss (graph 4, figure 7).

Glucose tolerance determinations on these obese cases indicate that some of them have a reduced glucose utilization, as has been previously reported.⁴ Others show a slight increase, or normal tolerance curve. Most patients with an initial reduced utilization of glucose manifest a tendency toward a more normal glucose tolerance curve after following this dietary treatment for four to six months, during which time there has been a reduction in body weight of 40 to 60 pounds (charts 1, 2, 3 and 4).

Hypertension was present as a complicating factor in a few of these patients before the onset of the weight reduction regime. The highest systolic pressure was 220 mm. of mercury. Blood pressure levels were checked from time to time to determine the effect of the high protein intake on this mechanism. No instance of either an increase in existing hypertension or an elevation in the normal blood pressure was observed during this dietary regime. On the contrary in some instances where hypertension initially existed, there followed an appreciable reduction in both systolic and diastolic levels after the body weight had been reduced by 30 to 60 pounds. Similar results have been observed in obese patients with hypertension following reduction in body weight by other methods.⁵

SUMMARY

No hormones or gland products known to therapeutics at this time are necessary adjuncts in the treatment of any type of obesity, excepting hypothyroidism.

A high protein, low fat, low carbohydrate, *ad lib.* diet, supplemented with vitamins and minerals, and with no calculation of caloric values, and without the administration of any known hormones, results in satisfactory weight reduction in all known types of obesity.

Endocrine obesity is a term which is misleading in that it conveys to the obese patient a false idea, suggesting that his obesity is due to some specific endocrine glandular deficiency which can be corrected by substitution endocrine, or hormone therapy. This causes the patient to seek needless endocrine medication, whereas dietary measures and reëducation of his faulty food habits are the true solutions to correction of obesity.

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A CLINICAL AND ELECTROCARDIOGRAPHIC STUDY OF PAROXYSMAL VENTRICULAR TACHYCARDIA AND ITS MANAGEMENT*

By GEORGE R. HERRMANN, M.D., and MILTON R. HEJTMANCIK, M.D.,
Galveston, Texas

A HEART that is damaged may be caused to fail by a suddenly developing rapid rate. Paroxysmal ventricular tachycardia is a relatively rare but as a rule a serious increase in heart rate originating in a temporary abnormal pacemaker in ischemic and damaged ventricular tissues. Most hearts in which abnormally augmented heart action develops in the ventricular muscle are those that have been previously damaged by circumscribed infarction, diffuse fibrosis, or digitalis poisoning. It is important to recognize and interrupt the rapid heart action promptly because the added strain will cause acute cardiac failure if it is allowed to continue. Furthermore, ventricular tachycardia may be the immediate precursor of ventricular fibrillation, as pointed out by Herrmann and Ashman^{1a} and by Wiggers.^{1b}

Myocardial infarction and toxicity from digitalis are generally considered the most common precipitating causes. Scherf and Kisch² emphasized the significance of previous myocardial damage as a prerequisite to the production of the disorder by digitalis. Occasional benign cases, with good prognosis, have occurred in young individuals with apparently normal hearts. Such cases have been noted in most comprehensive reports.

Diagnosis is made certain by the electrocardiographic criteria, which were first set down by Robinson and Herrmann.³ In a tachycardia with abnormally broad QRS complexes, the demonstration of an independent, usually slower, atrial rhythm establishes the diagnosis beyond question. Williams and Ellis⁴ observed that the P-waves may be difficult to demonstrate in the routine arm leads, and may be visualized more definitely in the precordial leads over the atria. Close resemblance of the form of isolated ventricular beats occurring before or after the paroxysms to the complexes of the tachycardia highly favor the diagnosis of tachycardia of ventricular origin. An atrial tachycardia with concomitant bundle branch block may be confusing. Cooke and White⁵ considered that onset of the tachycardia with an abnormal ventricular complex, or occurrence of a paroxysm of abnormal ventricular complexes during atrial fibrillation were each sufficient to establish the diagnosis. The clinical signs which should suggest the presence of ventricular tachycardia have been described by Levine.⁶

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From The Cardiovascular Service, University of Texas Medical Branch, Galveston, Texas.

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Our interest in paroxysmal ventricular tachycardia has recently been stimulated by the development of more promising methods of treatment for the control of the mechanism disorder in emergency situations and of subsequent management aimed at prevention of recurrences of the paroxysms. A study of the cases that we have recently controlled successfully and of all the cases that we have had in the Cardiovascular Service of the University of Texas seemed worthwhile. Besides the therapeutic data, we have assembled most of the pertinent information in these cases, and have summarized and tabulated the material.

THE PRESENT STUDY

A series of 20 cases of paroxysmal ventricular tachycardia has been analyzed, diagnosis in each being established by using the above cited electrocardiographic criteria. Of these 16 were seen in the John Sealy Hospital in the past 18 years, and four elsewhere. Three from the John Sealy Hospital were previously reported by E. H. Schwab.⁷ The average age of the patients was 52.8 years, the youngest being 18 and the oldest 80. Thirteen were between the ages of 45 and 65. There were 17 males and three females. Sixteen of the patients were white, two Mexican, and two colored.

The types of heart disease are summarized in table 1, which shows cor-

TABLE I
Etiology of Paroxysmal Ventricular Tachycardia
20 Cases

Acute myocardial infarction	8
(Hypertensive CV disease 4)	
Coronary sclerosis without infarction	6
(Hypertensive CV disease 2)	
Acute glomerulonephritis	1
Chronic rheumatic heart disease	2
Rheumatic heart disease with SBE	1
No organic heart disease	2

onary artery disease to be present in 70 per cent of the cases. Hypertension was present in six patients with coronary disease and in the one patient with atypical acute glomerulonephritis. The rôle of digitalis in precipitating the paroxysms is evaluated in table 2.

TABLE II
Rôle of Digitalis in 20 Cases of Paroxysmal
Ventricular Tachycardia

Definite toxicity	3
Probable toxicity	4
Moderate dosage	2
No digitalis	11

Fifteen of the cases were associated with signs of congestive failure, of which six had left ventricular failure alone, and the remainder had both right and left ventricular failure. In four instances the paroxysmal ventricular

tachycardia occurred with atrial fibrillation. Three patients showed cerebral manifestations, two due to the tachycardia itself and one secondary to cerebral embolism. One of these had generalized convulsive seizures, and another had attacks of syncope. Peripheral vascular collapse was observed in one patient, who died shortly after admission. Of the two patients with apparently normal hearts, one complained of precordial burning, and one had no complaints referable to the disorder.

The rates of the tachycardia varied between 110 and 220, with an average of 170. Three rates were below 150, and two were above 200. No correlation was observed between rate and prognosis, except that a continuous electrocardiogram taken during exitus of the patient with the slowest rate, of 110, showed slower and slower ventricular rhythm with periods of ventricular fibrillation, ending in asystole. Three cases were of the intermittent type, with runs of four to ten premature ventricular beats interspersed with atrial fibrillation in two instances and nodal rhythm in one. The duration of the paroxysms and results of termination are given in table 3.

TABLE III
Duration of Paroxysms with Results in Termination

Type	No. Cases	Reverted
Intermittent	3	2
Persistent	17	13
2-4 Hours	4	2
4-24 Hours	6	6
24-48 Hours	4	3
2-4 Days	2	2
6 Days	1	0

The results of emergency therapy in terminating the paroxysms are summarized in table 4. In three of the four patients receiving no specific

TABLE IV
Results of Treatment

Type Therapy	No. Episodes	Reverted
No specific	4	1 (3 died)
Oral quinidine	12	10
Intravenous quinidine	2	1
Intravenous morphine	2	1
Intravenous quinidine and digitalis	1	1
Intravenous morphine and carotid stimulation	1	1

therapy, the disorder persisted until death. Ten cases reverted on quinidine given orally, the amount required varying greatly, from 0.6 gram to 5.2 grams in 24 hours. The average given in the 10 cases in the 24-hour period before reversion was 1.5 grams, only four requiring over 2.5 grams. In one patient with acute myocardial infarction, the rhythm was not abolished with 11.8 grams of quinidine orally over a period of four days, and the patient died.

Two patients in critical condition following myocardial infarction were given intravenous quinidine. One had not responded to intravenous dosages of morphine of 11, 11, and 32 mg., and oral quinidine totaling 2, 5, and 3.3 grams on three successive days. This patient reverted to normal rhythm after 1.7 grams of quinidine sulfate was given by slow intravenous drip. Another patient, who was admitted in shock, showed no change in rhythm after being given 0.6 gram of quinidine sulfate intravenously in 10 c.c. of distilled water, and died in an hour. One case under treatment for subacute bacterial endocarditis was given 1.0 gram of quinidine sulfate intravenously in divided doses over a period of 12 hours, and then reverted to normal rhythm after the intravenous administration of 1.2 mg. Cedilanid. The intravenous administration of 16 mg. of morphine sulfate resulted in immediate cessation of the abnormal rhythm in one case with myocardial infarction. In another patient the ventricular tachycardia reverted to sinus rhythm on carotid sinus pressure six minutes after 45 mg. of morphine sulfate given intravenously, having previously been unaffected by repeated carotid sinus stimulation and 32 mg. of morphine sulfate.

TABLE V
Results of Treatment Re: Etiology

Type Heart Disease	No. Episodes	Reverted	Alive 1 Week
Acute myocardial infarction	8	5	3
Coronary sclerosis without infarction	6	4	4
Digitalis toxicity	7	6	1
Acute glomerulonephritis	1	0	0
Rheumatic heart disease	2	2	1
Rheumatic heart disease with SBE	1	1	0
No organic heart disease	2	2	2

In table 5 are listed the results attained in checking ventricular tachycardia in the various types of heart disease. It is notable that although six of the seven patients with digitalis toxicity had reversion of the tachycardia, all but one had died within a week. The two cases with no demonstrable heart disease were successfully treated, one with small and one with large oral doses of quinidine. The eight cases of myocardial infarction are analyzed in detail in table 6.

After reversion of the tachycardia, 12 patients were maintained on quinidine sulfate orally, in doses from 0.6 to 1.0 gram daily. One of these patients has been maintained on quinidine for six years without toxic or harmful effect, and without recurrence since the first year. In 10 cases paroxysmal ventricular tachycardia did not recur on this maintenance regime. However, four of these died within a week in spite of the established normal rhythm. Of the six other reverted cases, two are still alive, one after six months and one after six years. Two were discharged and not followed. One died three years later with cause of death unknown, and one died six weeks after reversion from another myocardial infarct. In one case even

TABLE VI

Detailed Analysis of Eight Cases of Acute Myocardial Infarction Complicated by Paroxysmal Ventricular Tachycardia

Age	Rate	Symptoms	Duration	Treatment	Result
56	176	Shock	2.5 hours	Quinidine gm. 0.6 intra-venously.	Not reverted, died 1 hr.
52	210	Left failure (mild)	24 hours	Quinidine gm. 0.6 orally.	Reverted. Maintained on quinidine. Died 3 yrs. later.
51	165	Left failure	2 days	No specific.	Not reverted. Died.
62	167	Right and left failure	1-2 days	Quinidine gm. 2.5 in 24 hours orally and digitalization.	Reverted. Died 2 days later with pulmonary infarction.
63	188	Right and left failure—mild	24 hours	Morphine sulfate mg. 15 intravenously.	Promptly reverted. Maintained on quinidine without recurrence. Died 6 wks. later. Another myocardial infarction.
54	150 intermittent	Right and left failure—mild	24 hours	Quinidine gm. 0.8 orally.	Reverted, did not recur on quinidine maintenance. Died wk. later. Pneumonia.
51	150	Right and left failure	6 days	Digitalized; quinidine gm. 3.5 per day for 2 days. Magnesium sulfate 2 c.c. 50% intramuscularly.	Not reverted. Patient died.
52	200	Right and left failure—mild	50 hours	Morphine sulfate 11, 11, 32 mg. intravenously with no effect. Quinidine orally gm. 2, 5 and 3.3 per day. Then quinidine gm. 1.7 intravenously.	Reverted after intravenous quinidine. Maintained on quinidine with no recurrence. Still alive, 6 months later.

small doses of quinidine were found to prolong the QRS complex over 25 per cent, and this patient has been effectively maintained on moderate doses of potassium iodide for myocardial sedation.

DISCUSSION

Since paroxysmal ventricular tachycardia usually occurs in patients with serious myocardial damage, it is at times difficult to ascertain to what degree the tachycardia per se is responsible for the signs and symptoms. It seems rational to consider the paroxysmal ventricular tachycardia an emergency situation in itself, and every attempt should be made to stop it and restore normal mechanism as soon as possible. The clinical improvement usually seen upon reversion has seemed to indicate that the seriously diseased heart is frequently barely able to support the increased burden imposed by the rapid rate. Mild to profound shock-like states that have been observed may well have resulted from decreased cardiac output due to inadequate diastolic filling. Cerebral symptoms may develop, on the basis of cerebral anoxia, as pointed out by Barnes.⁸

Precordial pain or discomfort is rarely a symptom of the ventricular tachycardia alone, according to Williams and Ellis.⁴ Usually, precordial distress is a part of the coronary thrombosis and myocardial infarction which has been complicated by the tachycardia. Impaired coronary filling and increased cardiac work incident to the tachycardia may actually aggravate the myocardial ischemia.

The danger of development of ventricular fibrillation in the presence of a ventricular tachycardia is well known. The longer the mechanism disorder is allowed to continue, the more likely is the appearance of ventricular fibrillation, since exhaustion of the myocardium increases its irritability.

Although supraventricular tachycardias may be stopped by methods which result in increased vagus tone, these methods are of little value in terminating a tachycardia of ventricular origin because the vagus nerves have little if any effect below the A-V bundle. Quinidine is effective in both atrial and ventricular tachycardias by virtue of its direct action on the heart muscle. It has come to be regarded as a specific in the control of paroxysmal ventricular tachycardia, although the dosage required varies greatly. Adequate dosage is to be stressed, as occasional patients require large amounts of oral quinidine before reversal. Before the actual reversal, a slowing of the tachycardia is generally noted, and in some cases this slowing alone may occasion some relief. Weisman⁹ demonstrated that an average single oral dose of quinidine produces a maximum concentration in the myocardium in about an hour, and is completely eliminated in eight hours. Excretion is thus rapid, and as pointed out by Gold,¹⁰ a fixed daily dose shows cumulation for only three or four days. Quinidine should be given orally in 0.2 to 0.4 gram doses each one to two hours until the abnormal rhythm is abolished. The largest dose in this series was 5.2 grams in 24 hours. Considerably larger amounts have been given for successful termination, as 7.5 grams in a day by Levine,⁹ and 12.3 grams in 2½ days by Reich.¹¹

Complications of quinidine administration have been reported, and objections to its use have been raised. It has been shown to actually produce ventricular tachycardia in rare instances, as in two cases reported by Hepburn and Rykert.¹² Kerr¹³ is skeptical of the value of quinidine in most ventricular tachycardias, questioning the part it has played in their termination. He believes it contraindicated in ventricular tachycardia after myocardial infarction because of the danger of producing ventricular fibrillation by further depression of a possibly damaged conduction mechanism. Schwartz and Jezer¹⁴ implicated quinidine as a causative factor in the production of transient ventricular fibrillation in two patients in whom the disorder also occurred spontaneously. In rare instances sudden death has resulted from quinidine therapy, on the basis of embolism at the time of reversion of atrial fibrillation, and of cardiac standstill caused by its depressant action. Frequent electrocardiograms are indicated to judge effectiveness of therapy and to anticipate serious untoward effects. Reich¹¹ emphasized the evaluation of the duration of the QRS complex to prevent serious

cumulative effects of quinidine, but the value of this criterion has been disputed by Zimmerman.¹⁵ Although we have had no fatalities which could be definitely ascribed to quinidine, we have been reluctant to administer it after the QRS complex has been prolonged over 25 per cent.

The intravenous use of quinidine has been favorably reported by Hepburn and Rykert,¹² with success in eight out of nine cases. Their method of administration, the same as used in the successful case in this series, consisted of dissolving 3.5 grams of quinidine sulfate in 500 c.c. of 5 per cent glucose, slightly warmed, and giving the solution intravenously at 100 to 120 c.c. per hour. The method is to be recommended when oral medications cannot be taken, when the condition of the patient is critical, and when oral administration has failed. We prefer to use quinidine lactate, which is more soluble and apparently as effective as other salts. Quinidine lactate is supplied in ampules of 0.65 gm. dissolved in 10 c.c. of sterile saline. Each ampule should be diluted with 50 c.c. of 5 per cent glucose solution and given slowly 1 to 2 c.c. per minute.

When digitalis is the probable precipitating factor, it should of course be withheld. Occasional cases respond only to quinidine and digitalization, as in one case of this series, and administration of digitalis is indicated in moderate to severe decompensation when it can be ruled out as a causative factor of the paroxysms. It would seem that small quantities of quinidine may be of value in preventing the appearance of the disorder whenever digitalization is necessary following myocardial infarction. The appearance of premature ventricular contractions in acute myocardial infarction would be a definite indication for prophylactic quinidine. If there is concomitant myocardial insufficiency and a digitalis preparation is given, quinidine most certainly is necessary. Ouabaine and digitoxin seem to be less likely to cause increased ventricular irritability and appear to be the preferable cardiotonics.

A maintenance dosage of quinidine after the rhythm has been abolished is highly desirable and almost imperative to prevent the return of the paroxysms. It should be continued for several days or weeks. The size of the dose must be adjusted for the patient. Some cases are controlled with small doses of 0.2 gram every six hours, while others may require larger doses more frequently administered. The reappearance of premature ventricular contractions is a sign of need for increased dosage, or resumption of therapy if it has been discontinued.

The intravenous use of morphine in the treatment of paroxysmal ventricular tachycardia has been advocated by Dr. Luis Gonzalez Sabathie of Argentina,¹⁶ who noted success in a case refractory to intravenous quinidine, and then achieved favorable results in nine out of 10 cases. He advised intravenous doses of 10 to 40 mg. repeated from a half to two hours. The mechanism of its action is obscure, as higher concentrations of morphine than can be attained clinically are required to affect the myocardium directly, according to Goodman and Gilman.¹⁷

Other drugs have been reported as successful in certain cases. Although their effect has not been consistent in terminating the paroxysms, their use may be considered in refractory ventricular tachycardias. The efficacy of intramuscular quinine hydrochloride has been reported by Riseman and Linenthal,¹⁸ and it may be tried as an alternative to quinidine. Levine⁶ has in rare cases noted restoration to normal rhythm upon a large subcutaneous dose of atropine while the rate is partially slowed by quinidine. Potassium chloride has been used with success orally, by Stempien and Katz,¹⁹ and Sampson and Anderson.²⁰ Intravenous magnesium sulfate has likewise been suggested, and was used with success in a case by Boyd and Scherf.²¹

SUMMARY

1. Twenty cases of paroxysmal ventricular tachycardia are analyzed with reference to type of organic heart disease and response to treatment. Acute myocardial infarction or digitalis toxicity was present in 15 of the patients, 14 having underlying coronary artery disease. Two cases were relatively benign, and occurred in patients with apparently normal hearts. Paroxysmal ventricular tachycardia develops most often in patients with extensive myocardial damage.

2. Electrocardiographic criteria for diagnosis are set down.

3. Complications of the paroxysms are discussed, with stress laid on the frequent emergency aspect and the desirability of early termination. In spite of reversion to normal rhythm and prevention of recurrence, the degree of underlying myocardial damage is frequently so severe that prolongation of life is only of short duration. The prognosis generally is serious.

4. Methods of therapy are summarized, with description of successes attained by oral quinidine, intravenous quinidine, and intravenous morphine. Results of maintenance dosages of quinidine in prevention of recurrences of the disorder are given. Adequate quinidine therapy is advocated in each case not showing toxicity or idiosyncrasy to quinidine. Maintenance doses of quinidine after reversion to sinoatrial rhythm are almost imperative as long as excess irritability of the myocardium exists. Intravenous morphine has recently shown favorable results, and seems to be worthy of trial before the use of any other drug.

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APPENDICITIS AND UPPER RESPIRATORY INFECTION: A REPORT OF 18 CASES AT SEA *

By GEORGE L. CALVY, Commander, M.C., U. S. Navy, *Great Lakes, Illinois*

A NAVAL escort carrier was engaged in shuttle operations between mainland and Southwest Pacific ports, carrying passengers, and following the Great Circle Route in its crossings.

Three epidemic waves of virus type "colds" were encountered in a three month period, synchronous with the appearance of an abdominal syndrome clinically indistinguishable from acute appendicitis. There were three distinct groups totaling five, four, and six cases respectively, whose periodicity corresponded with each upturn in incidence of upper respiratory infection. Three additional cases, occurring singly, were also admitted and are included in the series.

This was a curious experience, because, during an antecedent six month period, there had been no admissions for appendicitis.

EPIDEMIOLOGY AND CLIMATOLOGY

It is convenient to divide the total experience into three parts, conforming with the manifestations of the epidemic.

Phase I. The vessel was in mid-Pacific, approaching the International Date Line, having left Guam six days before. A decided change in climatic conditions had occurred and in the cooler environment perspiration had given way to increased urinary output. There had been no sick call visits recorded for "colds" or sore throats for 24 days, part of which period included liberty ashore in Japan. A few scattered colds appeared, then on successive days 20, 17, 28, 26, 22, 18, 33, and 21 men were treated for this affection.

Only one of the group seen was admitted to the sick list; the others were treated ambulant. As in subsequent phases, the upper respiratory manifestation was a naso-pharyngitis, accompanied by a thin, colorless, mucoid secretion. Mild to moderate malaise and low grade fever were other accompaniments. The affection was of short duration, 24 to 48 hours.

At the same time, five men were admitted whose chief complaint was right lower quadrant abdominal pain; all had experienced onset of symptoms within the same 48 hour period. In each instance, history of "head cold," preceding the abdominal distress, was given.

During this period at sea, there were 841 men aboard of whom 466 were ship's company and 375 were passengers. In addition, there were 44 of-

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Opinions expressed herein are those of the writer and do not necessarily represent the views of the Bureau of Medicine and Surgery, Navy Department.

ficers. As in the two subsequent phases, the abdominal syndrome appeared only among ship's company, sparing both passengers and officers. "Colds" were most uncommon among the latter two groups.

Both ship's company and passengers occupied living compartments in common and ate in the same mess as differentiated from the officer's environment of a separate mess and individual staterooms. One other group, the Hospital Corpsmen, lived separately, and they too were spared during this flurry.

Phase II. Eight weeks later, the vessel was moving westward toward Guam and in the same latitude and climatic environment. Another abrupt rise in upper respiratory infections occurred. Now, the factors of water balance were in reverse, with urinary output diminishing in favor of an increase in skin output.

Four men appeared with right lower quadrant abdominal pain and all but one cited "head cold" as forerunner of abdominal distress.

The population aboard was 720. Again, passengers were not affected. The sick call visitors this time were not those seen in the first wave of the epidemic.

Phase III. Two and one half weeks later, after the second phase had ebbed, it was common observation that a large number of people aboard had "colds." The ship was returning to the mainland and repeating events of the first phase.

In quick succession, six men were admitted with complaint of abdominal pain and placed under observation. All but one reported occurrence of rhinitis prior to onset of abdominal pain.

The total number of men aboard was 452 during this third phase, of whom 125 were passengers. This time, however, officers and corpsmen were also numbered among the victims though none of them suffered abdominal involvement.

MANAGEMENT

Each abdominal case was placed under the usual restrictive regime as regards alimentation and observed for 12 to 24 hours before decision was rendered. With no amelioration of general condition, surgical intervention was employed in 12 cases; the others exhibited improvement, were treated medically, and later discharged with the diagnosis, mesenteric lymphadenitis. Four of this latter group had recurrences and were re-admitted; after further observation and study, they were discharged.

CLINICAL DATA

Symptoms: In each instance, *pain* was the chief complaint, cramp-like, progressive in intensity, and localizing in the right lower quadrant. *Anorexia*, or disinclination to eat, was constant. Nausea was a major complaint but twice; none had vomited and none had resorted to self-medication. Constipation was present in five cases; diarrhea was absent. *Rhinorrhea* was

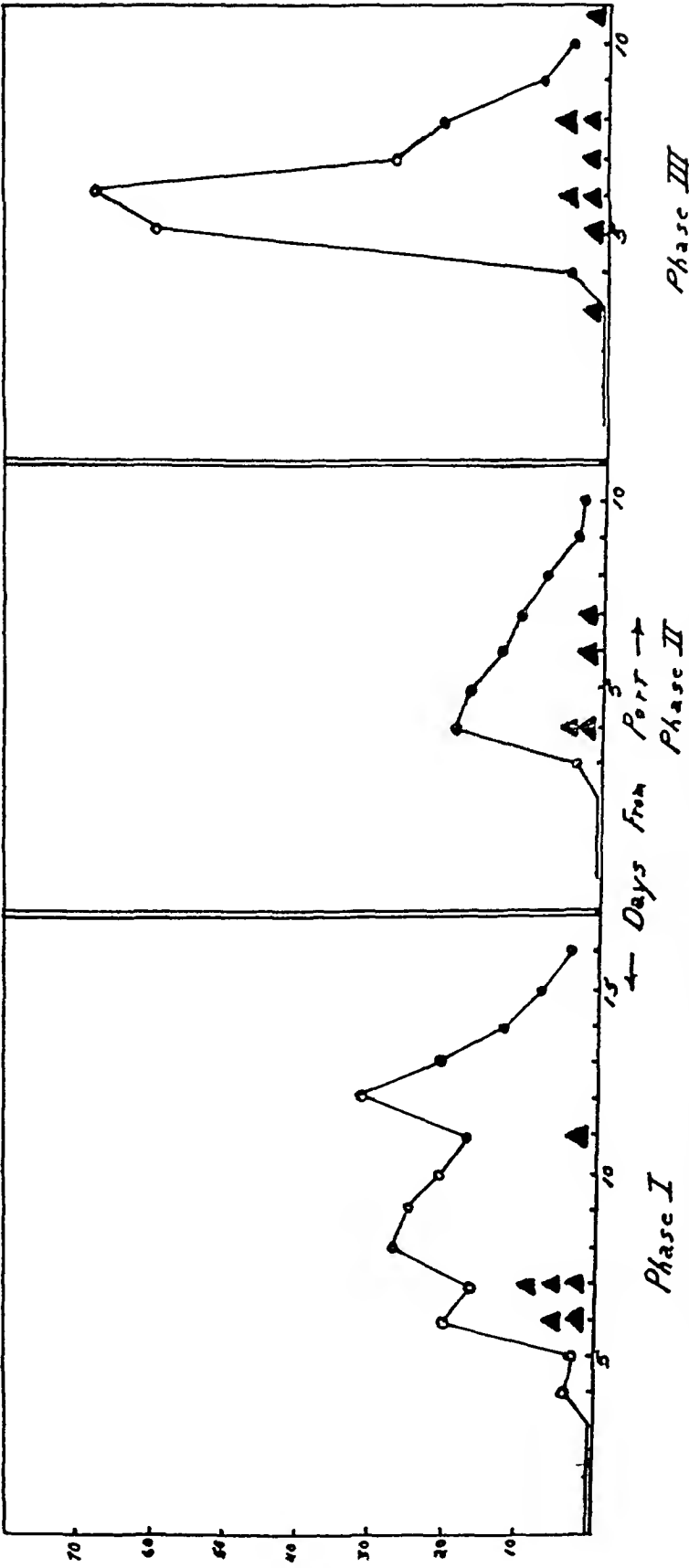


Fig. 1. Time relationship of abdominal syndrome and upper respiratory infection aboard ship. O = Upper respiratory cases/1000. ▲ = Case onset, abdominal syndrome.

cited in 16 of the 18 cases. In 14 instances, abdominal pain of similar character had been experienced previously, one or more times.

Signs: Localized tenderness and muscle-guarding over the site of the appendix was a constant finding; examination per rectum was contributory once. Temperatures were normal to moderately elevated, one temperature of 100° , two of 99.4° , two of 99.2° , and 13 normal temperatures being recorded on admission. Pulse rates varied widely with little correlation noted between rate and the severity of the affection.

Lymphoid System: Fifteen of the 18 possessed faucial tonsils. Lymphadenopathy pre-operatively was not noteworthy. Absent in every case was evidence of splenomegaly.

Age and Sex: The group was exclusively male, with an age range of 18 to 22, representing various divisions of the ship, with no department contributing disproportionately.

Constitution: No positive correlation could be drawn from factors of either race or constitution. It was a representative group that also included an Eskimo, Filipino, Indian, and Negro.

Laboratory Findings: Leukocytic indexes, both quantitative and qualitative, provided meager information. The total counts were within normal limits, with but two exceptions. Blood sedimentation rates were normal to moderately elevated. Urinalyses were essentially negative.

Gross Pathology: The appendixes were found in various positions, some freely accessible, others relatively inaccessible. All exhibited some evidence of acute inflammation, with conspicuous vascular engorgement and swelling. Free peritoneal fluid was present in four cases; plastic fibrinous exudate was noted seven times; enteroliths were contained in four appendixes, but without demonstrable evidence of causing primary obstruction; old adhesions were thrice noted. Regional (mesenteric) lymphadenitis was observed three times.

DIAGNOSIS

The reliable symptomatology of abdominal pain localizing in the right lower quadrant, fortified by the finding of localized tenderness and an essentially normal urinalysis, in the absence of pulmonary pathology, favored the diagnosis, acute appendicitis.

Two additional conditions figured in consideration of the diagnosis. Infectious mononucleosis was excluded in absence of its characteristic blood picture. Mesenteric lymphadenitis was considered in a differential light, and also as part of the total systemic response to a stimulus, characterized by lymphoid hyperplasia. That a similar process may affect the appendix merits attention when one considers the abundant disposition of lymphoid tissue in that organ.^{1, 2, 3}

DISCUSSION

An extensive literature has accumulated on the subject of appendicitis and any discussion of etiology must needs consider the many factors, single

or multiple, already proposed. Those due to mechanical and infectious factors remain in prominence.^{3, 4, 5, 6}

This report covers a period of one year aboard a naval vessel. During the first six months, appendicitis was absent; a few cases appeared thereafter, apparently dissociated from any environmental factor. The incidence rose abruptly with an outbreak of "colds," declined with subsidence of the epidemic, only to climb anew with each of two succeeding phases.

Inspection of food handlers and the mess disclosed nothing remarkable. The factor of crowding in living compartments, and its relation to droplet transmission of infection, was noted.

In the entire group of upper respiratory infections seen during this period, tonsillitis was absent. Throat smears yielded scant information. There was no basis for indictment of any of the streptococcal genera, rather did all evidence at hand point to a virus offender with entry presumably via the naso-pharyngeal portal.

Speculative evaluation of this total experience would perforce include queries on the selective character of involvement, with sparing of passenger complement; the time element, with the subtle implication of an incubation factor; rapid climatic change, with resultant physiologic imbalance.

It appears unlikely that an emotional component played a significant rôle; morale aboard was of high order, and the sick call journal, a reliable yardstick, reflected general well-being and freedom from "dis-ease."

SUMMARY AND CONCLUSIONS

1. An abdominal syndrome, clinically indistinguishable from acute appendicitis, was seen frequently in association with virus-type "colds."
2. Eighteen cases were admitted during a three month period, coinciding strikingly with three epidemic waves of upper respiratory infection.
3. These data suggest that, at least under some circumstances, there may be a close relation between an epidemic type of respiratory infection and the onset of acute appendicitis.

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FRIEDLANDER BACILLUS MENINGITIS: REPORT OF SEVEN CASES WITH TWO RECOVERIES *

By S. S. JACOB, M.D.,† and F. H. TOP,‡ M.D., F.A.C.P.,
Detroit, Michigan

IN the past 19 years there have been a total of 2879 cases of meningitis admitted to the Herman Kiefer Hospital. Of this total, there have been but five cases of Friedlander's meningitis. During the last 30 years at Henry Ford Hospital there have been 498 meningitis cases of which two were of the Friedlander type. Combining these two series gives a total of 3377 cases of meningitis of which only seven were attributed to the Friedlander bacillus. Stated another way, this organism was the etiological factor in approximately one out of every 482 cases or in 0.02 per cent. Ransmeier and Major ¹ collected a total of 30 cases from the literature up to 1943 to which can be added a case secondary to prostatic suppuration reported by Macky and Morris ² in 1943, another associated with liver abscess, pneumonia and empyema reported by Sheridan ³ in 1945, and one reported by Tartakoff, Grynbaum and Le Compte ⁴ in 1946 in which the meningitis followed removal of a meningioma from the right frontal area. If to these can be added the seven cases reported here, it will bring to 40 the total of reported cases.

Undoubtedly there have been other unrecognized and unreported cases but the conclusion is still inescapable that Friedlander's meningitis is a rare type, and because of this, it seemed worthwhile to report briefly seven cases.

Rothschild ⁵ has reported the only well substantiated case of Friedlander's meningitis with recovery prior to the use of the sulfonamide drugs. Meningitis in this case was secondary to otitis media, mastoiditis, and subdural abscess and recovery followed operation. Subsequent to the use of the sulfonamides, Lombard and Mondzain-Lemaire ⁶ gave an account of a case of head injury complicated by a mixed meningeal infection with recovery following sulfonamide-chrysoidine therapy. Montea and Real ⁷ related a case in a two year old in whom the primary focus could not be ascertained. This case was treated with sulfapyridine and recovery ensued. Robertson's ⁸ case in which diabetes was a complicating factor was successfully treated with sulfapyridine. A case in which meningitis was secondary to sinus infection was reported by Kolmer and Rule. ⁹ This patient showed initial improvement but relapsed and died on the eighth day of sulfapyridine therapy. Sulfadiazine therapy resulted in recovery in the case treated by Julianelle. ¹ Trevett, Nelson, and Long ¹⁰ report another successfully treated with this drug by Hodes.

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† From the Henry Ford Hospital and the Herman Kiefer Hospital, Detroit, Michigan.

‡ From the Herman Kiefer Hospital, Detroit, Michigan.

Our cases are summarized as follows :

Case 1. G. G., a 47 year old white male, was admitted on January 1, 1930 with typical signs and symptoms of meningitis. The spinal fluid showed 640 cells of which 82 per cent were polymorphonuclear and many Gram-negative bacilli which were determined to be Friedlander's bacilli. A blood culture was negative. Anti-meningococcic serum was given initially before the organism was identified, otherwise purely symptomatic therapy was used. The patient's condition grew progressively worse; facial paralysis developed on the third hospital day, and death occurred the following day. Autopsy revealed a purulent meningitis and a lobular pneumonia. Culture of the brain exudate and the right lung both showed *Bacillus mucosus capsulatus*.

Case 2. J. H., a 49 year old colored male, was admitted on February 20, 1933 with characteristic symptoms and signs of meningitis. He had received "blood treatment" in December, 1932 but on examination the blood Wassermann test was negative. The spinal fluid cell count was 2040 of which 84 per cent were polymorphonuclears. Large Gram-negative bacilli (Friedlander's) were found in both the spinal fluid and the blood. The fever remained 104° or over, and death ensued 18 hours after admission. Treatment consisted of anti-meningococcal serum and symptomatic care. Autopsy showed a purulent meningitis, a three centimeter abscess in the right frontal lobe, suppurative right otitis media, and purulent osteochondritis of one rib.

Case 3. F. B., a 39 year old colored male, was admitted on February 12, 1937 with a history of diabetes for five years; he had also received "blood treatments" weekly for the past two years. Both ears had been discharging since January 1, 1937. On February 9, 1937 he developed meningeal symptoms and signs. An initial spinal fluid examination showed only seven cells but Friedlander's bacilli grew on culture. On February 13 a second spinal fluid specimen showed 160 cells, mostly polymorphonuclear, and large Gram-positive and Gram-negative bacilli. The fasting blood sugar was 270; the urine showed four-plus sugar. The Kahn test was three-plus. The patient failed to respond to insulin and intravenous glucose and saline. Death occurred 39 hours after hospital admission.

Case 4. A. G., a 55 year old white male, was admitted in a comatose condition on April 23, 1946 with a history of fever since April 21 and bilateral chronic ear infection with deafness of eight years' duration. Signs of meningitis were present on admission and a purulent discharge from both ears was noted. The spinal fluid cell count was 620, polymorphonuclears comprised 60 per cent; and type A Friedlander's bacilli were found on culture. A blood culture was negative. Culture of the discharge from the ears showed Friedlander's bacilli type A, identified by the finding of large Gram-negative encapsulated rods on smears and by the 'Quellung' reaction with specific Friedlander's type A serum.

Treatment consisted of intravenous sulfadiazine and penicillin intramuscularly in presumably adequate therapeutic doses. On the fifth hospital day streptomycin was given, 1/10 mg. twice daily intrathecally and 1.8 mg. in divided doses every two hours intramuscularly up to the time of death at which time 8.5 mg. had been given.

Roentgenograms showed chronic sclerotic mastoiditis bilaterally and the presence of an aortic aneurysm. The blood Kahn test was three-plus. A left sided paralysis developed on April 25 and the patient grew progressively worse until death occurred on the ninth hospital day. Autopsy revealed a five centimeter brain abscess in the right temporal lobe with rupture into the right ventricle, purulent meningitis, bilateral chronic mastoiditis, purulent tracheobronchitis, bilateral lobular pneumonia and aortic aneurysm.

Case 5. A. P., a 50 year old white male, was admitted on September 6, 1946 with a history of a "cold" for three days. The evening before admission the patient had a sudden excruciating headache, stiff neck, and pain in the left ear. A past history

indicated frequent colds; a family history brought out that two sisters had died of tuberculosis.

Physical examination revealed a semi-stuporous, critically ill man in considerable pain. The right pupil was larger than the left, the discs normal. The right ear canal was distorted, a watery exudate was present, the ear drum was not visible, and a mastoidectomy scar was apparent. The left ear drum was injected, bulging but intact. The neck and back were moderately stiff. The deep reflexes were hypoactive but equal, the Babinski was negative and no paralysis or weakness was noted. Petechiae were not seen.

The spinal fluid showed 3300 cells, of which 85 per cent were polymorphonuclears, a three plus Pandy test, total protein and sugar determinations of 100.5 and 57 mg. per 100 ml. respectively, and a negative smear and culture for organisms. Two separate cultures of the spinal fluid obtained from a second lumbar puncture done the day after admission were both positive for Friedlander's bacillus type A and, in addition, one of these showed *Staphylococcus albus* which was believed to be a contaminant. A blood culture was negative. The white blood cells fell from 12,000 on admission to 9300 on the sixth day. The organism was identified in this case by finding large Gram-negative encapsulated rods and by the 'Quellung' reaction with a specific known Friedlander type A serum.

A roentgenogram of the chest was negative and those of the mastoids showed the sclerosis and indistinct cell outline of an old chronic mastoid infection on the left side. A provisional diagnosis of meningitis secondary to chronic otitis media, mastoiditis, and brain abscess was made and penicillin in doses of 50,000 units was administered intramuscularly every three hours until the seventh hospital day. Sulfadiazine was also given from the time of admission until the fourth hospital day when the occurrence of crystalluria and hematuria necessitated its discontinuance. The patient became afebrile on the second hospital day, headache and earache disappeared and stiffness of the neck had decreased by the fourth day. The bulging left ear drum subsided without rupture or incision. The patient had no complaints from the fifth hospital day on to the time of discharge on the eleventh hospital day.

Case 6. M. B., a 53 year old white female, was admitted on September 22, 1927 with a history of dizziness, internal strabismus and double vision following reopening of a mastoid cavity on September 19, and fever, headache and vomiting the day of admission. A bilateral radical maxillary and intranasal frontal sinus operation had been performed on December 10, 1925. A mastoidectomy on January 29, 1927 uncovered mastoiditis and subperiosteal and extradural abscesses. A Gram-negative bacillus of the Friedlander type was recovered on culture from the mastoid area. The mastoid required re-opening on June 30, 1927 and on September 12, 1927.

Physical examination on present admission showed a right mastoidectomy scar and a right internal strabismus but no stiffness of the neck was noted. The patient improved until September 25 when signs and symptoms of meningitis developed. Therapy consisted of analgesics, sedatives, intravenous glucose, and blood transfusions. The spinal fluid cell counts varied from 1100 to 2724 and Friedlander's bacilli were repeatedly cultured from the spinal fluid and blood. Despite therapy the patient's condition grew progressively worse and death occurred on the ninth hospital day.

Case 7. A. H., a 56 year old white female, was admitted on August 2, 1944 with a history of headaches, of two years' duration. A tooth was extracted two months before admission following which the right ear became swollen and very painful. Two weeks later the ear drum ruptured and much pus was released. The drainage stopped but the ear continued to pain her. Two days before admission the patient had marked nausea, vomiting, dizziness, blurred vision and fainting spells. The day before admission she had a chill. A sulfonamide of undetermined type and dosage was given.

No other history was recorded. Physical examination revealed an obese female with atrophic nasal mucous membranes, infected tonsils, fine crepitant râles at the base of the left lung, an umbilical hernia and varicose veins of both legs.

Laboratory findings were as follows: There was a four-plus urinary sugar; a blood sugar determination of 228 mg. per 100 ml.; a blood non-protein nitrogen of 23.5 mg. per 100 ml.; a negative blood Kline test; and a leukocyte count of 5250. Protamine and regular insulin rapidly brought the diabetes under control. On August 7, 1944 severe headache, fever of 102°, and vomiting developed; herpes simplex developed on August 10. The spinal fluid on this date contained 700 cells (type unrecorded), with 64 mg. sugar per 100 ml. and 75 mg. protein per 100 ml.; gave a negative Kahn test; showed Gram-negative bacilli and also a few Gram-positive cocci on smear and culture. Penicillin, in a dose of 100,000 Oxford units, was given intrathecally and 12,500 units intramuscularly every three hours until 200,000 units had been given at which time the organism was shown to be resistant to it in vitro. Then sulfadiazine was used in a dosage of 4 gm. stat and 1 gm. every four hours from August 12 through August 19. Penicillin was again started on August 25 but replaced by sulfathiazole which in turn was replaced by sulfadiazine. The sulfonamide blood level varied between 2.7 and 9.3 mg. per 100 ml. during this period. The laboratory reported Gram-negative bacilli apparently encapsulated showing a very mucoid growth with cultural characteristics of Friedlander's bacillus and a few organisms showed positive Neufeld reaction with Friedlander's anti-serum type A.

Roentgenograms showed a chronic mastoiditis. A mastoidectomy on August 28, 1944 revealed a moderate amount of granulation tissue with little cellular destruction; a mastoid culture demonstrated no growth in seven days. On August 31 the right antrum was washed and foul smelling pus obtained from which Gram-negative organisms and Gram-positive cocci grew out in 48 hours. On August 23 the spinal fluid showed 110 cells with lymphocytes predominating and no organisms on smear or culture. On August 25 the patient became worse and the spinal fluid cell count rose to 1530 with 93 per cent lymphocytes. The spinal fluid showed 200 cells on August 31; 36 cells on September 8; and only nine cells on September 19. An antrum window was made on the right side on September 15 and much pus and polypoid material was obtained. The patient was discharged on September 22 apparently recovered after a hospital stay of 51 days. She was seen again on October 18, 1944 when she had excess cerumen removed from the right ear.

COMMENT

In our series there were seven cases, and previously recorded cases number 33, giving a total of 40 cases in all, which is not an imposing number upon which to judge factors such as age, sex, and color. However, when a condition such as Friedlander's bacillus meningitis has been nearly 100 per cent fatal, clinical characteristics are of some interest and value. A comparison of the previously reported cases is made with a group of seven here reported with reference to the following characteristics: *Age*: Of the previously reported cases, 10 were under four years of age; 23 were over 15 years old; none were in the age group from 5 to 14 years. In the present group of seven cases, the ages vary from 39 to 56 years. *Sex*: Friedlander's meningitis has been reported more than twice as often in males as in females. There were five males and two females in the group of seven cases. *Color*: More cases have been reported among the white race than among others. There were five white and two colored in this group which when considered

in terms of the proportion of colored in the population (9 per cent) does not bear out previous experience. However, the number of cases is too small for a definite statement.

Spinal fluid findings: Cultures of the spinal fluid from the initial punctures were positive in the majority of cases reported. In the authors' series, direct smears and cultures were positive in five cases; two were negative on direct smear; one gave no growth; and in one case, no report of a spinal fluid culture was obtained. *Blood cultures:* A positive blood culture is apparently indicative of a poorer prognosis than when the blood culture is negative. The two recovered cases had negative blood cultures. Of the remaining five who died, the blood culture was positive in three, negative in one, and there was no record of a blood culture in one case. *Probable primary focus:* In over half of the adult cases, the middle ear, mastoid, or sinuses were the probable primary foci. In our series, the middle ear alone

TABLE I
The Age in Relationship to the Probable Primary Focus
40 Cases of Friedlander's Bacillus Meningitis

Probable Primary Focus	Age Groups					Total
	0-4	5-14	15-34	35-54	55-74	
Ears and mastoid	1		2	5	4	12
Paranasal sinuses			1	3	1	5
Pharynx			1	1		2
Lung	2		1	1	2	6
Liver					1	1
Uterus (?)			1			1
Prostate					1	1
Joint	1					1
Unknown	6		1	3	1	11
Total	10	0	7	13	10	40

was the probable focus in three cases; the middle ear and the mastoid together in two cases; while in the remaining two cases the primary focus was unknown. Debilitating chronic diseases such as syphilis, diabetes, and alcoholism may predispose to the development of Friedlander's meningitis. The patients of Weischselbaum,¹¹ Renon and Blamontier,¹² Rothschild,⁵ Menetrier and Bertrand-Fontaine,¹³ were found to have sugar in the urine while Robertson's⁸ patient was a known diabetic. Adding the two cases reported in this article, it is noted that seven of the 40 cases, or 17.5 per cent, had evident diabetes or had glycosuria. Brunner,¹⁴ found cirrhosis of the liver in the case of Friedlander's meningitis reported by him and Ransmeier, and Major's¹ case showed carcinoma of the prostate. Alcoholism was thought to be a factor in some cases. Beitzke¹⁵ and Papandrea's¹⁶ cases had congenital syphilis. Two of the seven cases reported here were known syphilitics. Intracranial hemorrhages were found in two newborn infants with the disease.

The diagnosis is suggested by finding organisms with the characteristics of Friedlander's bacillus in direct smear but confirmed only by positive cultures obtained from the spinal fluid. The clinical symptoms and signs are indistinguishable from those of meningitis caused by other types of virulent organisms. Friedlander's meningitis appears to be no longer a disease which is invariably fatal. In the recovered cases reported here combined sulfadiazine and penicillin therapy appears to have aided recovery as did streptomycin in cases of bronchiectasis and ozena, reported by Herrell and Nichols,¹⁷ in which the apparent causative organism was the Friedlander's bacillus. The effectiveness of the treatment of experimental infections with the Friedlander group in mice, as reported by Heilman,¹⁸ lends support to the use of streptomycin in meningitis of this type in man. In view of these results, it is suggested that the combined administration of large doses of sulfadiazine, penicillin and streptomycin be tried in future cases of the disease.

SUMMARY

Recorded instances of Friedlander's bacillus meningitis are relatively few. An additional group of seven cases is added to the available literature on this infection. The combined administration of large doses of sulfadiazine, penicillin and streptomycin is recommended in the treatment of Friedlander's bacillus meningitis.

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ADRENO-SYMPATHOGENIC HEART DISEASE (NEUROHORMONAL FACTORS IN PATHO- GENESIS AND TREATMENT) *

By W. RAAB, M.D., F.A.C.P., *Burlington, Vermont*

MOST of the non-congenital and non-infectious forms of heart disease are generally attributed to mechanical factors, such as the "burden," "load," "strain" of high blood pressure in "hypertensive" heart disease or to impairment of coronary blood flow in "arteriosclerotic" heart disease. In either one of these conditions a relative or absolute deficiency of the myocardial oxygen supply is believed to exist and to contribute essentially to functional and ultimately structural lesions of the heart.

Little or no emphasis is being put on the fact that the typical clinical features of "hypertensive" heart disease are not infrequently found without hypertension and those of "arteriosclerotic" heart disease without any significant degree of arteriosclerosis.

It has become a firmly established tradition among clinicians and pathologists to explain myocardial anoxia exclusively on the grounds of a demonstrable or assumed discrepancy between myocardial mass or mechanical work on one side and coronary blood flow on the other. Almost no attention is being paid to the pathogenic rôle of the most powerful and ever present potentially heart-anoxiating chemical agents of the body, namely the sympathomimetic amines of the epinephrine-sympathin group.

Before a discussion of the basic importance of these substances in the development of certain heart diseases will be attempted, the following fundamental points should be stressed:

(1) Epinephrine is a specific oxidation catalyst.^{1, 2, 3} It intensifies the myocardial oxygen consumption^{4, 5, 6, 7} to a degree which exceeds both the oxygen demands made by simultaneously increased muscular action and the increase of oxygen supply due to simultaneous coronary dilatation.^{8, 211} In other words, epinephrine is capable of causing myocardial anoxia as a specific metabolic effect, regardless of hemodynamic conditions and regardless of the volume of coronary flow.

(2) Sympathomimetic amines (epinephrine, sympathin) are constantly formed not only in the adrenal medulla but also in the sympathetic ganglia^{9, 11p} from where they are discharged through postganglionic neuro-secretion directly into the respective effector cells, e.g. the myocardium.^{11p, 192, 193,}

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From the Division of Experimental Medicine, University of Vermont, College of Medicine, Burlington, Vt.

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184, 185, 212, 221 Furthermore, the brain contains and discharges into the circulation a sympathomimetic amine (encephalin) which acts upon the cardiovascular system like epinephrine.²²⁰

(3) The heart muscle possesses an outstanding ability to absorb epinephrine from the circulating blood and to accumulate it in a slightly modified form with the catechol nucleus remaining intact (probably sympathin).^{11a, p}

(4) The metabolic changes elicited in the heart muscle by epinephrine injection (intercellular edema, anoxia, diminution of creatine, phosphagen and adenylypyrophosphoric acid)^{12, 13, 14} are identical with those found in experimentally anoxiated animal hearts,^{15c, 210} in diseased human hearts^{16, 17, 18, 19, 20} and in animal hearts after strenuous exercise.^{15a, c}

(5) The electrocardiographic signs of myocardial anoxia, as produced by injection of epinephrine or nor-epinephrine (sympathin), are essentially analogous to the "strain" type and "coronary insufficiency" type of the human electrocardiogram.^{23, 24, 25, 26, 222} Their occurrence depends on the development of certain metabolic changes in the myocardium as outlined in point (4)^{15c} but not on hemodynamic factors (blood pressure, heart rate).²²²

(6) Sympathetic neurosecretion directly into the heart muscle, as well as adrenal medullary secretory discharge is followed by an accumulation of

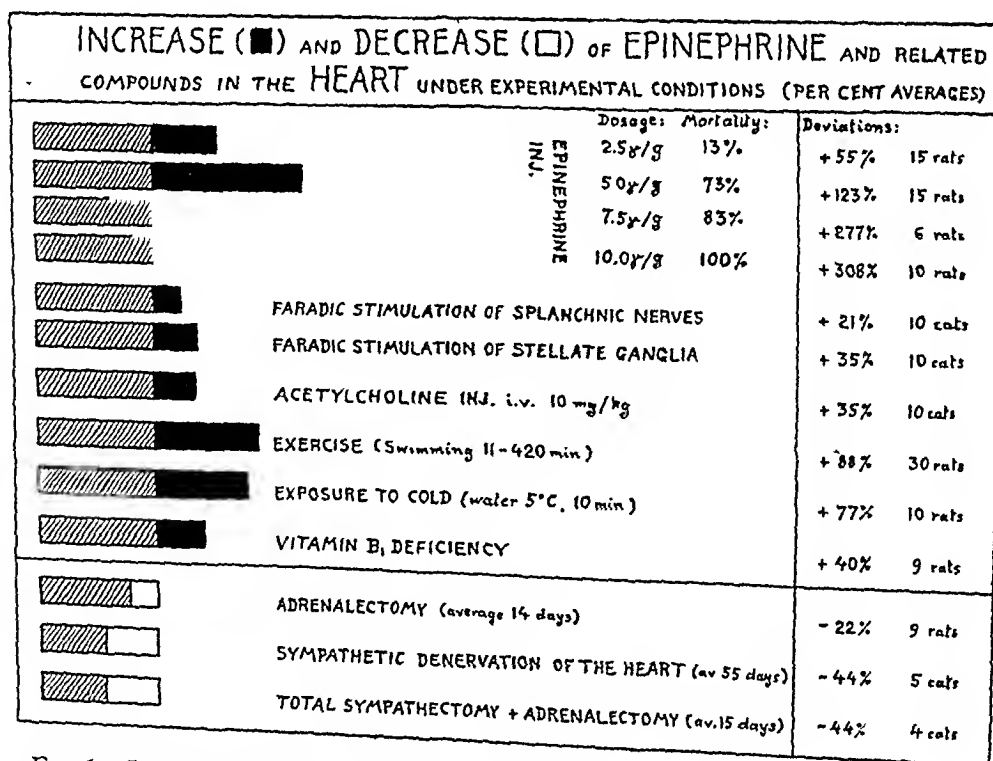


FIG. 1. Influence of various experimental conditions, involving either increased or decreased adreno-sympathetic neurosecretory activity, upon the epinephrine-sympathin content of the heart muscle.^{11a, p, q, s, v} The results in this graph and in the following ones are expressed in color units, each unit equalling the color intensity of 0.001 gamma of epinephrine. (Regarding the specificity of the method see Biochem. Jr., 1943, xxxvii, 470 and 11p.)

sympathin and epinephrine in the myocardial cells.^{11a, p, q} Such adreno-sympathetic discharges occur physiologically under various conditions^{11a} (e.g. physical exercise, exposure to cold (figure 1), intense emotions, etc.) which are known to be detrimental to the aging and damaged heart and which are often accompanied by the electrocardiographic manifestations of myocardial anoxia.^{27, 28, 29, 188, 184, 185}

Age seems to be an important factor, insofar as the average concentration of epinephrine-like material (sympathin) in the human heart muscle was found to increase markedly with advancing years^{11b} (figure 2).

Pathological adreno-sympathetic secretory discharges occur in persons with tumors of the adrenal medulla (pheochromocytomas) or sympathetic paragangliomas or probably in case of a general constitutional hyperirritability of the adreno-sympathetic system which can exist without any morphologically detectable pathology.

In the following the relationship between excessive epinephrine-sympathin secretion or sensitization on the one hand and common cardiac syndromes on the other will be pointed out.

(a) ANGINA PECTORIS

One of the most conspicuous peculiarities of the anginal syndrome is its immediate causal connection with adreno-sympathetic neuro-secretory activity. For this there is ample evidence:

(1) The attacks occur ordinarily under the very conditions which are known to be accompanied by sympathetic stimulation and by discharges of epinephrine,³⁰ and to be followed by an accumulation of epinephrine-like material (sympathin) in the heart muscle,^{11a} namely physical exertion, exposure to cold (figure 1) and emotions.

(2) Typical attacks can be provoked by the injection of epinephrine^{25, 31, 32} even in healthy individuals,^{11c, 33} and by the administration of agents which stimulate the adrenosympathetic system, e.g. tobacco smoking^{34, 35, 36} or large doses of insulin.^{11d, 38, 39, 40, 41, 42, 43}

(3) Attacks of anginal pain are common in patients with tumors of the adrenal medulla^{44, 45, 46}; they were found to be accompanied by an increase of the blood epinephrine level⁴⁰ and to disappear after removal of the tumor.^{45, 46}

(4) An abnormal elevation of the epinephrine-sympathin level of the blood was regularly observed also in patients with angina on effort immediately after physical exercise tests^{11e *} (figure 3).

* In some earlier publications the results obtained with Shaw's colorimetric method for "adrenalin"-determination, as modified by the writer, were erroneously interpreted as indicating "adreno-cortical compounds." This had to be modified subsequently when it was found that cortical steroids do not directly participate in the readings and that the latter consist of epinephrine and related catechol compounds, such as sympathin. Ascorbic acid contributes also to the colorimetric readings but its color intensity is so weak that it does not greatly affect the results (see Biochem. Jr., 1943, xxxvii, 470).

(5) The electrocardiographic changes occurring during anginal attacks are analogous to those elicited by the administration of epinephrine^{24, 26, 31} and of nor-epinephrine (sympathin).²²²

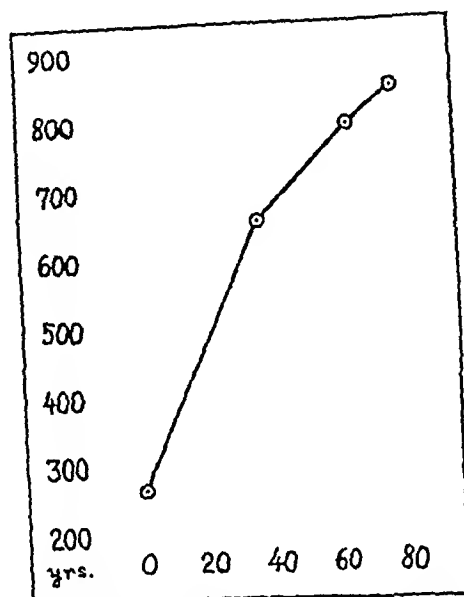


FIG. 2. Increase of the myocardial epinephrine-sympathin concentration with advancing age. (The figures represented in this curve are averages of a total of 60 human hearts, subdivided into four age groups.)^{11b}

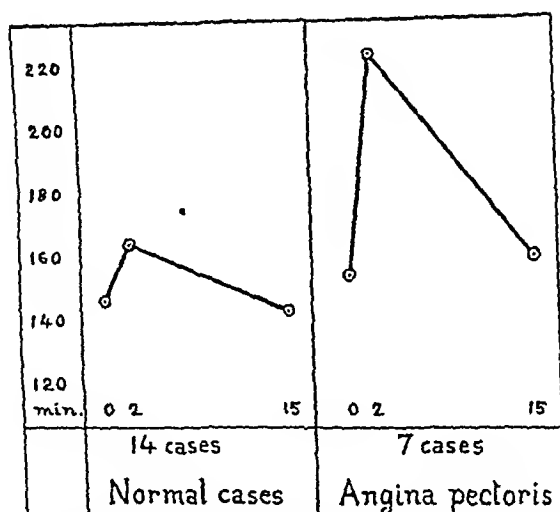


FIG. 3. Reaction of the average blood level of epinephrine-sympathin to physical exercise (climbing stairs) in normal persons and angina patients.^{11c} (Compare also figure 11 and figure 7.)

Two objections have been raised against the theory that angina on effort, etc. be due to acute adreno-sympathogenic anoxia of the heart. One is the coronary-dilating effect of epinephrine, as seen in various mammals. Apart from the fact that the assumption of a coronary dilatation through epinephrine in the human heart has been contradicted,⁴⁷ it appears unlikely that

such an effect should take place in hardened, sclerotic coronary vessels. Furthermore, even maximal coronary dilatation does not suffice to compensate for the specific myocardium-anoxiating action of excess amounts of epinephrine-sympathin.⁸

The second objection, interpreting the rapid therapeutic effect of nitroglycerine as proof of relaxation of a coronary "spasm," is unfounded in view of the desensitizing effect against epinephrine-sympathin which nitroglycerine exerts upon the heart muscle itself¹¹⁹ (figure 14) and in view of the lack of any evidence in favor of the spasm concept.

It is obvious that hearts with sclerotic, narrow coronary vessels will be particularly prone to suffer from an additionally anoxiating acute adreno-sympathetic influx. However, the angina-producing effect of overdoses of epinephrine, as it has been observed in young individuals without coronary sclerosis,^{110, 33} suggests that this latter condition is not an indispensable prerequisite for the occurrence of genuine adreno-sympathogenic angina pectoris.

(b) SUDDEN CARDIAC DEATH WITHOUT SIGNIFICANT MORPHOLOGICAL PATHOLOGY

One of the easiest and quickest ways rapidly to produce fatal cardiac failure in experimental animals is the injection of epinephrine. Death occurs inevitably in rats if the myocardial concentration of epinephrine-like material exceeds the sharply defined critical maximum level (1900 col. un./gm.^{11a}). It is usually preceded by gasping and pulmonary edema.^{11f}

In man, sudden, unexpected death has been frequently observed in cases of tumors, hemorrhages and other pathological changes of the adrenal glands.^{48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 144} Sudden death has also repeatedly been caused unintentionally by injection of epinephrine,^{11g, 58} and numerous sudden deaths without explanatory morphological findings have been reported as having occurred under circumstances which were strongly suggestive of a coincidence with adreno-sympathetic neuro-secretory discharges, namely emotional shock^{59, 60, 61, 62, 63, 64, 224} or strenuous physical exercise.^{65, 66, 67, 68, 69, 70, 71, 72} Ventricular ectopic pre-fibrillation rhythms which are believed to commonly precede sudden cardiac death^{196, 197, 198} can be induced in man by epinephrine injection.¹⁹⁶

In two cases of sudden, otherwise unexplained death of young persons with morphologically normal hearts, the only postmortem finding, apparently incompatible with survival, was the presence of an excess concentration of epinephrine-like material (sympathin) in the myocardium^{11g, h} (figure 4).

It seems very probable that most of the hundreds of sudden deaths among young soldiers which have been reported in recent years^{71, 72} and many more similar cases were due to such fatal myocardial sympathin accumulations, as morphological alterations of the coronary vessels were often entirely absent or too insignificant to account for a fatal myocardial anoxia.^{72, 196} Many of

these deaths were preceded by anginal pain. In 69 out of 140 cases of death without significant postmortem findings, there was evidence of pulmonary congestion⁷² which is a manifestation of acutely exaggerated adreno-sympathetic stimulation.^{187, 188}

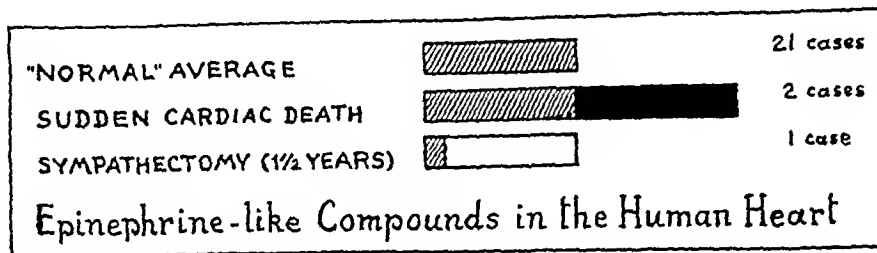


FIG. 4. The black area indicates excess adrenalin-sympathin above the normal average, the white area indicates a diminution from the normal average.—The term "normal" refers to the hearts of persons who had died from non-cardiac causes.^{11a, p, h}

Probably the first historically recorded instance of sudden death of a healthy young soldier under physical and emotional adreno-sympathetic strain is that of the famous Marathon runner who collapsed dead after having reached Athens and after having shouted the news of the victory over the Persians. It took 2434 years to come to a plausible explanation of his dramatic end.

(c) THYROTOXIC HEART DISEASE

The phenomenon of sensitization of the heart to epinephrine and to sympathetic stimulation through the thyroid hormone has long been known.^{73, 74, 75, 76, 77, 78} Accordingly, the critical fatal level of myocardial epinephrine-sympathin concentration was found to be markedly lowered in thyroxin-treated animals^{11/} (figure 5).

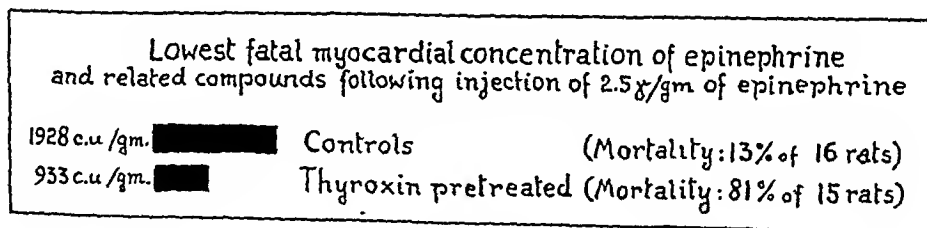


FIG. 5. Increase of epinephrine toxicity to the heart through thyroxin.^{11/} (Compare also figure 13.)

Since evidence of an increased adrenal secretory activity in thyrotoxicosis is lacking, it appears probable that many typical features of the thyrotoxic heart (tachycardia, tendency toward auricular fibrillation, electrocardiographic changes of the anoxic type¹⁸⁰) are due largely to the thyroxin-potentiated effects of epinephrine-sympathin reaching the heart muscle from outside. Furthermore, it has recently been shown²¹² that the sympathin

production in the heart itself is increased under the influence of the thyroid hormone.

Some workers^{79a, 80, 81, 100} have suggested that the ultimate congestive cardiac failure, occasionally occurring in "thyro-cardiac" patients, may be attributable to a vitamin B deficiency which often co-exists with thyrotoxicosis.⁸² This view appears to be supported by observations discussed in the following paragraph.

(d) BERIBERI HEART DISEASE

The hearts of thiamin-deficient animals contain excessive amounts of epinephrine-like material (sympathin)¹¹⁰ (figure 1) which disappear promptly as soon as thiamin is supplied.¹¹⁰ Increased epinephrine-levels were also found in the blood of thiamin-deficient animals.⁸³

The characteristics of the human beriberi heart, e.g. the anoxic electrocardiogram,^{84, 85, 86, 87, 88, 200} the tendency toward congestive failure and pulmonary edema,^{89, 91} degenerative structural changes of the myocardium,^{89, 90, 91, 92, 93, 200, 201} the "pistol shot" pulse and the exaggerated epinephrine sensitivity of beriberi patients^{89, 94} are all strongly suggestive of a significant involvement of the adreno-sympathetic system in the pathogenesis of the cardiovascular syndrome of beriberi.

The presence of excessive amounts of acetylcholine (which is the physiological stimulant of adreno-sympathetic neuro-secretion¹⁰⁴) in the hearts of thiamin-deficient animals⁹⁵ may explain the apparent intensification of adreno-sympathetic activity in beriberi as a secondary phenomenon. Furthermore, the hypertrophy of the adrenal cortex in beriberi^{96, 97, 98} can be regarded as a possible contributory factor toward sensitization of the heart to epinephrine-sympathin.^{111, 121}

(e) "HYPERTENSIVE" HEART DISEASE

The period of "nephro-totalitarianism" which had almost completely dominated the conception of arterial hypertension in the Western hemisphere during the past decade has gradually gone beyond its climax, both because of lack of evidence of a purely or prevailingly renal mechanism in most forms of clinical hypertension^{99, 100} and because of accumulating positive indications of the decisive involvement of neurogenic factors.¹¹⁴ Among these indications the therapeutic results of radical sympathectomy^{101, 102} and the experimental production of arterial hypertension through artificially induced ischemia of the brain^{103, 104} are perhaps the most striking.

As far as cardiac pathology is concerned, there are numerous clinical, pathological and experimental facts which point toward a biochemical, combined adreno-sympathogenic and adreno-cortical mechanism of "hypertensive" heart disease:

(a) The typical clinical, electrocardiographic and myocardial structural features of "hypertensive" heart disease are commonly present in patients

with medullary or cortical tumors of the adrenal glands, regardless of the presence or absence of arterial hypertension.^{48, 119, 120, 123, 124, 125, 182} Adrenal cortical hyperplasia or cortical adenomas are frequently found in hypertensive individuals.^{155, 156} A relationship of adrenal cortical function with exaggerated, heart-damaging adreno-sympathetic action is suggested by the epinephrine-potentiating effect of the cortical hormones^{111, 121, 230} (figure 6). Furthermore, desoxycorticosterone favors the accumulation of epinephrine-sympathin in the heart muscle.^{11a}

Desoxycorticosterone tends to increase the intracellular sodium concentration in the myocardium¹²² and an abnormally increased intracellular sodium concentration has also been found in the hearts of patients who had succumbed to congestive heart failure.²¹

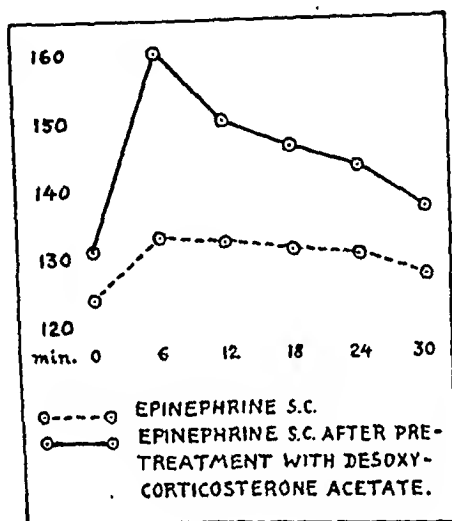


FIG. 6. Intensification of the blood pressure effect of subcutaneously injected epinephrine (av. 0.45 mg.) by pre-treatment with desoxycorticosterone acetate (av. 150 mg. in av. 5 days). This effect as well as the provocation of anoxic changes of the electrocardiogram through desoxycorticosterone exemplifies the potentiation of adreno-sympathetic phenomena in the cardiovascular system through cortical steroids.¹¹¹

(b) The blood level of epinephrine-sympathin in persons with uncomplicated essential hypertension is normal at rest^{11k} but abnormally high elevations of these substances in the blood occur frequently following physical exercise.^{11k} * (figure 7). This suggests an exaggerated excitability of the adreno-sympathetic neurosecretory system and may possibly be connected with peculiarities of the muscular valve mechanism of the adrenal veins which have been described in hypertensive individuals.^{111, 112}

The amount of sympathonimetic amines excreted with the urine ("uro-sympathin") is usually increased in hypertensive persons.²¹⁸

(c) The electrocardiographic features of "hypertensive" heart disease closely resemble those elicited by sympathetic stimulation or epinephrine

* See footnote p. 1012.

injection,^{105, 106, 107, 108} or injection of desoxycorticosterone acetate,¹¹¹ especially regarding changes of the T waves. Also an occasional shortening of the PR interval¹⁰⁹ belongs in the category of sympathogenic effects.

(d) Degenerative and fibrotic changes of the myocardium which are common phenomena in advanced "hypertensive" heart disease, are similar

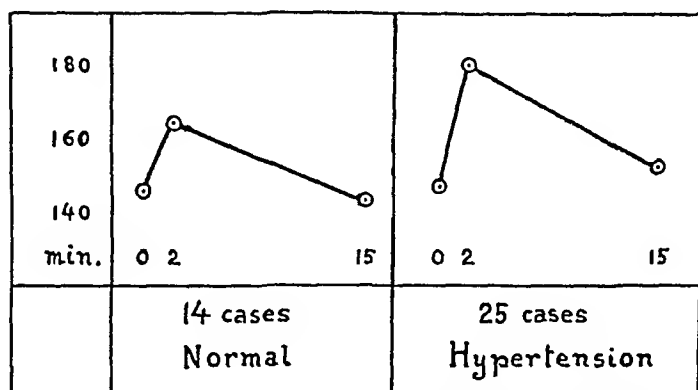


FIG. 7. Reaction of the average blood level of epinephrine-sympathin to physical exercise (climbing stairs) in normal persons and patients with hypertension.^{111c} (Compare also with figure 3.)

to those artificially produced by frequently repeated injections of epinephrine in animals^{49, 113, 114, 115, 116, 117, 163} and man,¹¹⁸ by administration of desoxycorticosterone^{122, 147} and of acetylcholine,²³⁵ the natural agent inducing adreno-sympathetic neurosecretion.¹⁹⁴

(e) Abnormally high concentrations of epinephrine-sympathin were found in more than one half of the hearts of patients who had died from "hypertensive" heart disease.^{11a}

(f) Sympathectomy in animals was found to be followed by a marked diminution of the amount of epinephrine-sympathin in the myocardium,¹¹⁸ and in the heart of a sympathectomized hypertensive patient an extremely low concentration of these products of adreno-sympathetic neurosecretion was likewise observed.^{11a}

(g) Striking normalizations of the pathological electrocardiogram occur in clinical arterial hypertension soon after radical sympathectomy, even if the patients remain hypertensive.^{108, 110 *} On the other hand, the characteristic effects of injected adrenaline on the electrocardiogram were found to be independent of the blood pressure reaction and could be elicited even when the vasopressor action was abolished by pretreatment with benzodioxane or dibenamine.^{222, 229}

These facts seem particularly significant. They strongly suggest that it is not merely the mechanical "burden" of an elevated blood pressure which causes the electrocardiographic "strain" pattern but that the latter is largely attributable to an excessive influx and activation of anoxiating epinephrine-

* Figures 6, 10 and 3, 5, 6, 10 of the respective papers.

sympathin from areas of adreno-sympathetic neurosecretion. Surgical denervation deprives these structures of their secretory function.^{11p, 8}

(h) Hearts, showing marked hypertrophy of the left ventricle, with or without degenerative myocardial changes, have been observed in a considerable number of instances without any evidence of hypertension or coronary sclerosis, both in children and adults.^{202, 203, 204, 205, 206, 207} Since the characteristic pathological phenomena of this non-hypertensive form of "hypertensive" heart disease are experimentally reproducible by chronic epinephrine and desoxycorticosterone intoxication,^{113, 122, 147} a causal rôle of excessive adreno-sympathetic and adreno-cortical activity seems probable also in this syndrome of "idiopathic" cardiac hypertrophy. It often terminates in sudden cardiac death.^{203, 206, 207}

It may be mentioned here that comparatively large amounts of a sympathomimetic amine ("encephalin") with epinephrine-like cardiovascular effects have been discovered in the brain,²²⁰ especially in the basal ganglia, whence a part of them passes into the cerebrospinal fluid and probably into the general circulation. Elevations of the blood pressure and anoxic changes of the electrocardiograms, as observed after war injuries to the brain,¹⁰¹ may be attributable to the entry of such sympathomimetic substances from the injured brain areas directly into the blood stream.

It is true that the phenomena of "hypertensive" heart disease are frequently coördinated to the hypertensive state and that they may be seriously aggravated by it but they constitute essentially a primarily biochemical and not a hemodynamic problem. Adreno-sympathogenic metabolic "strain" of the heart muscle can exist, regardless of the height of the blood pressure level. Conversely, its roentgenological and electrocardiographic signs have been seen to disappear under dietary treatment without a proportionate reduction of the blood pressure.^{231, 232}

Exaggerated joint adreno-cortical and adreno-sympathetic coöperation seems to be a decisive pathogenic factor in "hypertensive" heart disease with or without hypertension.

(f) UREMIC HEART DISEASE

In the advanced stages of various forms of uremia (glomerulonephritic, pyelonephritic, nephrosclerotic, obstructive, mercury poisoning) the blood contains regularly excessively high concentrations of an epinephrine-like substance (figure 8) with intensely cardiotoxic sympathomimetic properties, as tested on the isolated frog heart (figure 9) and on the electrocardiogram of the rabbit in which it proved rapidly fatal (figure 10).¹¹¹ The hearts of uremic persons show, likewise, excessively high, obviously fatal concentrations of this material (figure 8). Its origin is not yet definitely known. In view of the fact that sympathomimetic amines, such as epinephrine, sympathin and oxytyramine, are normally excreted by the kidneys in a modified form,^{126, 127, 218} it appears possible that epinephrine-sympathin, deriving from

adreno-sympathetic neurosecretory discharges all over the body, accumulates in the blood due to renal excretory insufficiency.

The appearance of sympathomimetic cardiotoxic material in the blood is roughly paralleled by increasing anoxic electrocardiographic changes analogous to those produced by epinephrine^{111, 128, 129, 130, 131, 132} and ultimately accompanied by other manifestations of possibly adreno-sympathetic origin, such as progressive cardiac failure, pulmonary edema and death. In the heart muscle of uremic persons severe degenerative changes were frequently reported^{130, 133, 134, 135, 136} as well as a diminished creatine concentration¹³⁷ in analogy to the effects of toxic doses of epinephrine.¹²

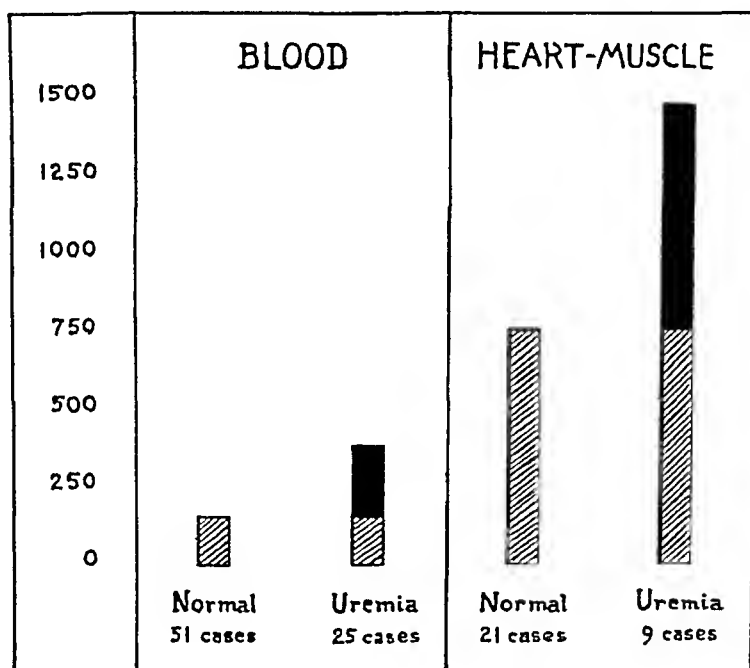


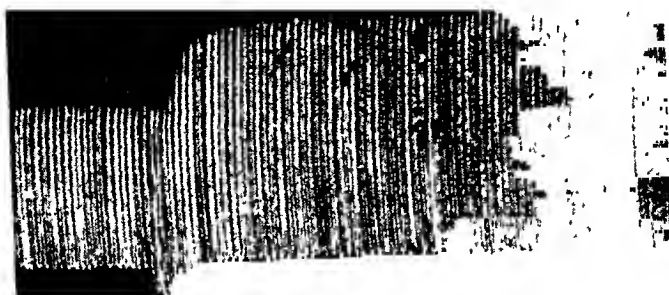
FIG. 8. Average concentrations of epinephrine-like compounds (probably epinephrine-sympathin) in the blood and heart muscle of uremic patients.¹¹¹

Although it is recognized that other abnormal constituents of the uremic blood, such as an excess of potassium^{138, 139, 140} and cardio-inhibitory phenol compounds^{129, 141, 142, 189} may also contribute to cardiac damage and death, the accumulated adreno-sympathogenic material appears to be of considerable significance.

(g) CORONARY SCLEROSIS

The question of adreno-sympathogenic factors in the origin of sclerosis of the coronary arteries is intimately linked up with that of the pathogenesis of arteriosclerosis in general. Besides the well-known destructive effect of epinephrine on the muscular media of the arterial walls, it is noteworthy that the atheromatous deposition of alimentary cholesterol in the intima of large vessels is also markedly accelerated and intensified through epinephrine.^{111, m,}

¹⁴³ The sympathetic innervation of the arteries supplies their walls with a direct influx of epinephrine-sympathin and the epinephrine-sympathin content of the human aorta was found to increase with advancing age.^{11b} The highest concentration was observed in the sclerotic aorta of a case of cortical



Ringer ↑ Serum A.C. ♀ 26 yrs
AC 475 col un./cc
NPN 123 mg% Creat. 6 mg%
Bl.pr. 224/120 mm



Ringer ↑ Serum ↑ Ringer

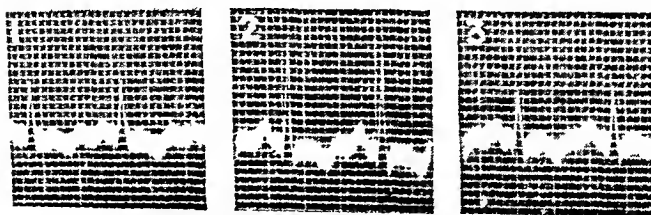


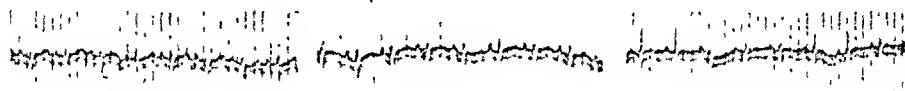
FIG. 9. Epinephrine-like effect of uremic serum upon the isolated frog heart. The electrocardiogram is that of the patient whose serum was used in this test.^{11f}

adrenal tumor.^{11b} The production of marked vascular lesions through repeated implantation of adrenal tissue^{145, 146} or through administration of cortical sterols^{147, 148} which intensify the cardiovascular effects of epinephrine^{11f, 121, 230} suggests a coöperation between the adrenal cortex and the adreno-sympathetic system in the origin of arteriosclerotic changes.

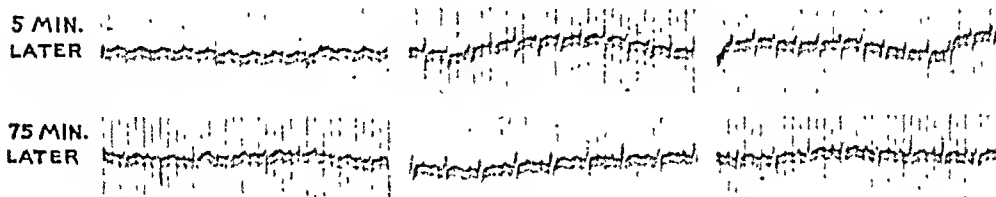
Coronary sclerosis in particular could be experimentally produced by letting cholesterol-fed animals run in a treadmill.¹⁴⁰ Since physical exercise is accompanied by a marked accumulation of epinephrine-sympathin in the heart^{11a} and since epinephrine favors the development of atheromatosis,^{11m} a causal connection seems probable also regarding this phenomenon.

RABBIT. - I.V. INJ. OF ALCOHOLIC EXTRACTS OF BLOOD SERA

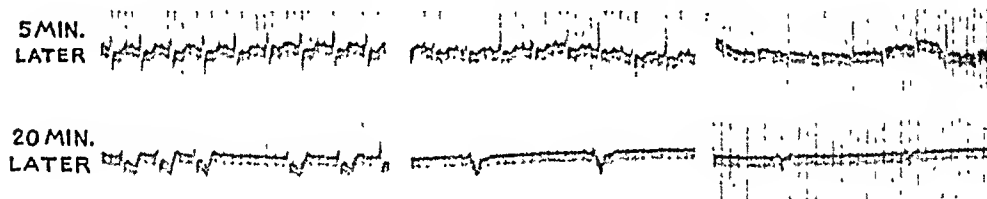
BEFORE INJECTION:



NORMAL SERUM (EXTRACT OF 10 cc.):



UREMIC SERUM* (EXTRACT OF 10 cc.):



* ♂ 34 yrs. - BLOOD AC 305 col.un./cc, NPN 172 mg%, Bl.Pr. 215/130 mm.

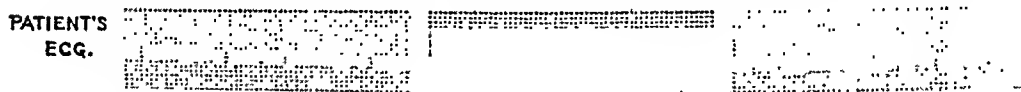


FIG. 10. Effect of intravenous injection of protein-free extracts of normal and of uremic serum upon the electrocardiogram of the rabbit. Death followed two minutes after the last electrocardiogram. The human electrocardiogram at the bottom is that of the patient with uremia whose serum was used in this experiment.¹¹⁷

In the light of the above outlined considerations, coronary sclerosis and angina pectoris on effort, etc. would appear as coördinated and mutually aggravating but not necessarily interdependent conditions of basically adreno-sympathetic neurosecretory origin.

(h) THERAPEUTIC CONSIDERATIONS

Recognition of the adreno-sympathogenic background of the forms of heart disease discussed in the preceding paragraphs permits the retrospective establishment of a patho-physiological rationale for some widely used thera-

peutic procedures as well as the systematic search for new methods of treatment.

The following guiding principles should be kept in mind in such endeavors: (a) Prevention or suppression of excessive adreno-sympathetic activity; (b) desensitization of the heart to the pathogenic effects of epinephrine-sympathin through correction of a sensitizing hormonal situation or through administration of adreno-sympatholytic drugs.

The first-named aim can be achieved by the surgical removal of pheochromocytomas or of paragangliomas or of the epinephrine-sympathin-producing and -discharging nervous apparatus of the heart (ganglionectomy, sympathectomy, pericoronary neurectomy). Such procedures have proved successful in the abolition of anginal attacks,^{46, 213, 214, 215} of the electrocardiographic signs of myocardial anoxia^{108, 110, 213} and of cardiac enlargement.¹⁵⁰ The beneficial results of sympathetic surgery in angina pectoris are usually attributed to the severance of afferent sensory fibers alone because the anoxiating neurosecretory function of efferent sympathetic cardiac fibers is not taken into consideration.

Non-surgical measures with an analogous purpose are the use of sedatives and the recommendation of physical and emotional rest which are intended to minimize the central stimuli for adreno-sympathetic neurosecretory activity.

Roentgen irradiation of the adrenal glands diminishes adrenal medullary secretion^{11a} and was found to abolish the characteristically exaggerated adreno-sympathetic discharges in angina pectoris patients^{11c*} (figure 11).

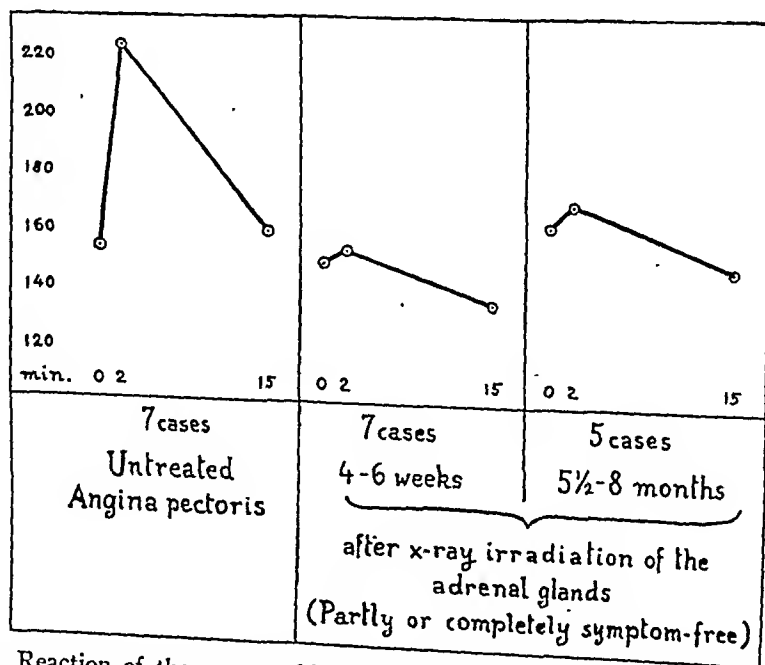


FIG. 11. Reaction of the average blood level of epinephrine-sympathin to physical exercise (climbing stairs) in angina patients before and after clinically successful x-ray treatment over the adrenal glands.^{11c} (Compare with figure 3.)

* See footnote p. 1012.

It proved therapeutically efficient in the majority of adequately treated cases^{11c, v, 151, 152, 153, 208, 225, 227} and it is often followed by a normalization of the anoxic electrocardiogram at rest as well as exercise.^{11c, t, 151a, 154} The favorable results last usually for years.^{11c, v} Roentgen irradiation directed toward the thoracic sympathetic nerves has likewise been described as being of therapeutic value.^{178, 179, 180, 181}

Desensitization of the heart to epinephrine-sympathin through elimination of the sensitizing thyroid hormone is the rationale for the etiological

E.P. ♀ 63 YRS. ANG. PECT. FOR 7 YEARS.

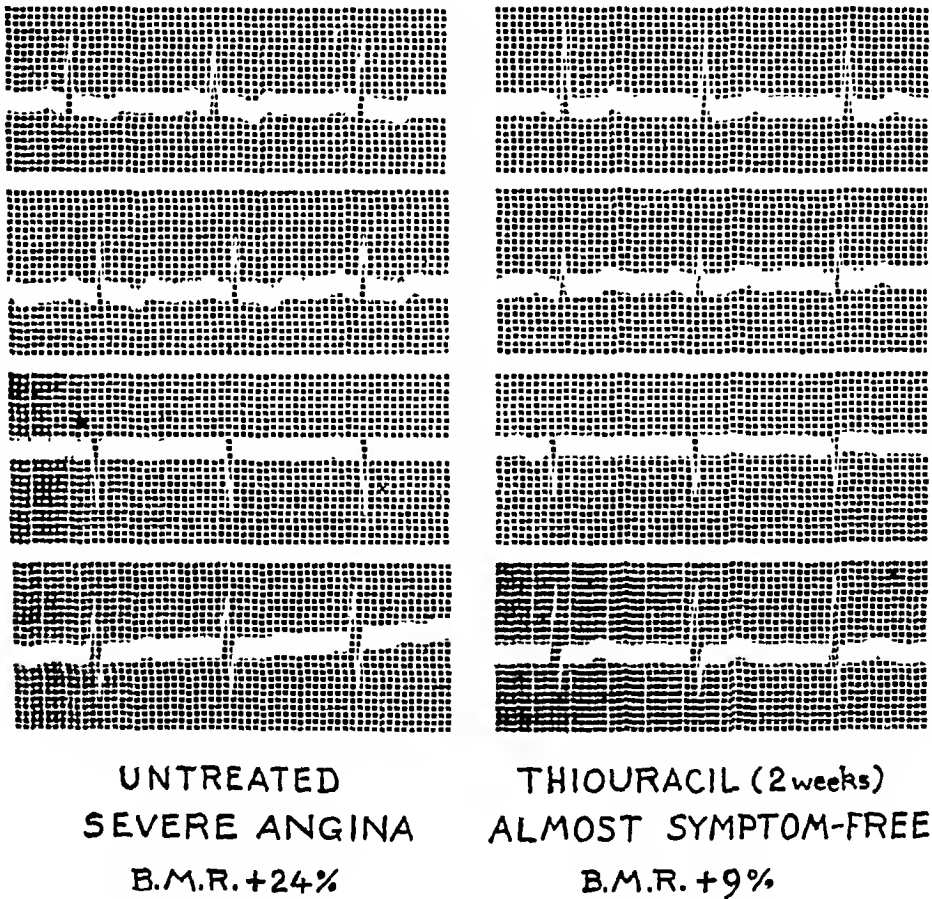


FIG. 12. Normalization of the electrocardiogram of a patient with severe angina pectoris through thiouracil.¹¹ⁿ

treatment of thyrotoxic heart disease by thyroidectomy or thiouracil. Striking therapeutic results have been obtained also in angina pectoris through surgical^{157, 158, 159, 190} or medicinal (thiouracil^{11n, 160a, b, 161, 209, 210, 223, 226}) inactivation of the thyroid gland (figure 12). Thiouracil, which will probably be superseded by the almost non-toxic propyl-thiouracil,¹⁶² diminishes or abolishes the anoxiating effect of epinephrine on the heart, as manifested in the electrocardiogram,^{11o} and was found to markedly elevate the lethal level of

epinephrine-sympathin concentration in the hearts of animals¹¹⁷ (figure 13). Thyroidectomy proved also helpful in certain cases of congestive heart failure.¹⁵⁷

Highest tolerated myocardial concentration of epinephrine and related compounds following injection of 5.0 g/gm of epinephrine		
1636 c.u./gm	Controls	(Mortality: 43% of 15 rats)
3111 c.u./gm	Thiouracil pretreated	(Mortality: 7% of 14 rats)

FIG. 13. Increase of epinephrine tolerance of the heart through thiouracil.¹¹⁷
(Compare also figure 5.)

The reported value of the administration of testosterone propionate in angina pectoris^{164, 165, 166, 167, 168, 169, 170, 171, 172} may be explained as an analogy to the normalization of the epinephrine-like metabolic changes in the hearts of castrated animals which was observed when the male sex hormone was administered.¹⁵⁶ In anginal conditions during the menopause the treatment with estrogens has been found effective¹⁷³ for probably similar reasons.

Adreno- and sympatholytic agents, such as Fourneau's 833F and 933F, priscol, dibenamine hydrochloride and dihydroergotamine, some of which proved spectacularly heart-protecting in animals¹¹⁷ (figure 14) have been

MAXIMUM TOLERATED MYOCARDIAL CONCENTRATION OF EPINEPHRINE and related compounds following injection of epinephrine in rats pretreated with:		
	0	1900 c.u./gm
	933 F	2134 " " "
	Priscol	2903 " " "
	Dibenamine HCl	12742 " " "
MORTALITY (per cent) AFTER INJECTION OF EPINEPHRINE (10 mg/kg) in rats pretreated with:		
	0	100 %
	933 F	44 %
	Priscol	10 %
	Dibenamine HCl	0 %

FIG. 14. Protection of the heart against the lethal effect of large doses of epinephrine (10 mg/kg.) through adreno-sympatholytic drugs.¹¹⁷

tried only on a very small scale in clinical heart disease, so far. Favorable results with 833F¹⁷⁴ and with dihydroergotamine²¹⁶ in angina pectoris cases have been reported but these drugs would deserve a much more extensive clinical testing. Ergotamine preparations proved capable of normalizing

the electrocardiogram in certain forms of angina pectoris²³³ but their use may be accompanied by untoward side effects.²³⁴

It should be reëmphasized that nitroglycerine as well as papaverine, which diminishes myocardial oxygen-consumption,²²⁸ counteract the effects of epinephrine-sympathin directly in the heart muscle¹¹⁹ (figure 15) and that their therapeutic action in angina pectoris^{175, 176} is probably to be attributed to this mechanism rather than to a dilatation of allegedly spastically contracted or of sclerotic, hardened coronary vessels. It has recently been stated that the effect of drugs upon the heart should not be evaluated according to

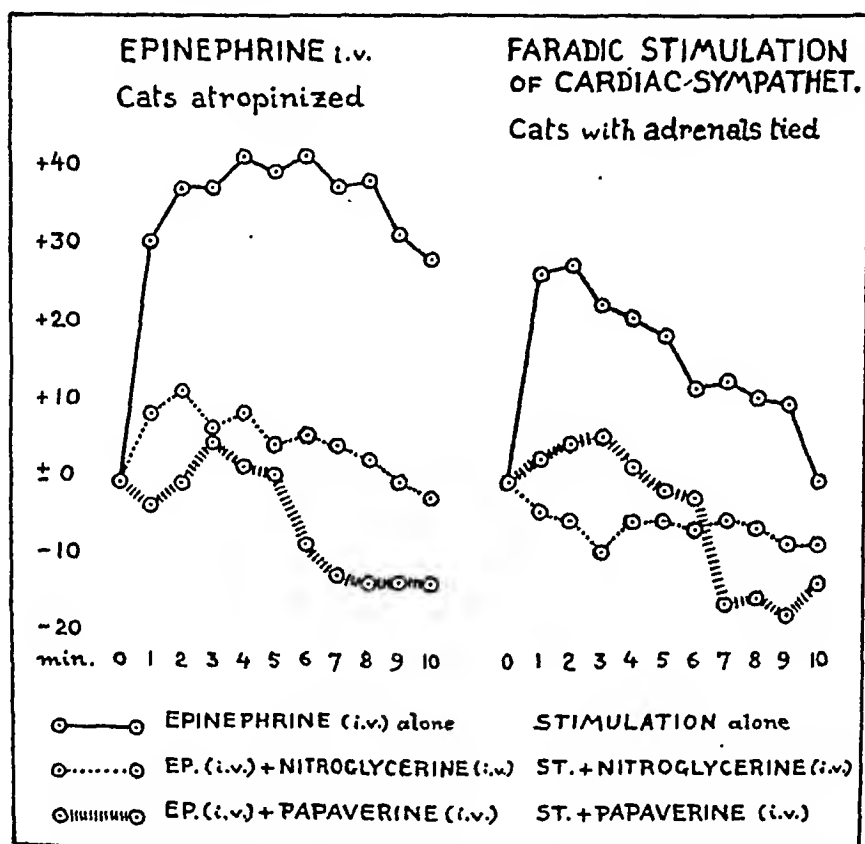


FIG. 15. Average heart rate responses of 10 cats each in 6 experimental groups demonstrating the antagonistic effect of nitroglycerine and of papaverine against continuously infused epinephrine and against sympathin accumulating in the heart muscle during prolonged faradic stimulation of the stellate ganglia.¹¹⁹

their influence on coronary flow but rather according to their effect upon the relationship between oxygen delivery and myocardial oxygen demand.²¹⁷

The apparent rôle of electrolytes in heart disease, especially the accumulation of sodium in the myocardium under the influence of adrenal cortical steroids, makes the therapeutic effect of certain sodium- and lipid-free dietary regimes¹⁷⁷ intelligible.

COMMENT

Developments in the biochemical and physiological laboratories around the world have led to results of fundamental significance for the interpretation

of cardiac chemical pathology and its neuro-hormonal background. Integration of these numerous but widely scattered experimental findings with clinical facts was rarely attempted on a broad basis. One of the reasons for this side-by-side existence of clinical and experimental investigation with only fragmentary reciprocity may have been the traditional belief of clinicians and pathologists that mechanical dynamics and coronary flow of the heart, "the pumping and the plumbing," as a young critic expressed it, are the ultimate ratio from which all pathological cardiac phenomena can be more or less satisfactorily explained. Epinephrine is still considered in most clinical textbooks as a "drug" of some therapeutic value but of little other significance; the neuro-secretory, epinephrine-sympathin-producing and -discharging activity of the vegetative nervous system and its biochemical implications in cardiac pathology, especially the specific heart-anoxiating effects of epinephrine and sympathin, are scarcely mentioned and the existence of severe, even fatal, functional cardiac anomalies without visible morphological pathology is discussed only with reluctance, if at all, in the clinical literature.

The coördination of at least one elementary aspect of neuro-hormonal physiology with cardiac pathology, as attempted in this study, may be arbitrary in some details and it calls for more elaborate consolidation in every single point but it is believed to constitute a necessary step toward a deeper understanding of the origin of heart disease and toward new rational therapeutic ventures.

CONCLUSIONS

The following points have been discussed:

The function of epinephrine as an oxidation catalyst; the specific heart anoxiating effect of epinephrine (sympathin) regardless of hemodynamics and coronary flow; the influx into the heart muscle of sympathomimetic amines (epinephrine, sympathin) both from the circulating blood and from the supplying sympathetic nerve terminals; their functional potentiation through the thyroid hormone and the adrenal cortical hormones; their increased accumulation in the heart muscle under conditions of sympathetic stimulation and with advancing age; their pathogenic effects upon myocardial metabolism, structure and electrocardiographic manifestations; the fatal effect of their excessive accumulation in the heart above a definite critical threshold, acute or chronic.

The conditions under which epinephrine and sympathin appear to be excessively discharged (paragangliomas, angina pectoris with or without coronary sclerosis, sudden cardiac death without morphological pathology) or excessively activated (thyrotoxic heart) or excessively produced and activated ("hypertensive" heart with or without hypertension, beriberi heart) or excessively retained in the blood and myocardium (uremic heart).

The physiological rationale for some older as well as newer forms of

cardiac therapy is deducted: (a) desensitization of the heart muscle to epinephrine-sympathin (thyroidectomy, thiouracil, nitroglycerine, papaverine, adreno-sympatholytic drugs); (b) suppression of excessive adreno-sympathetic stimulation and neurosecretion (removal of pheochromocytomas and paragangliomas, sympathectomy, roentgen irradiation of adrenal glands and sympathetic plexus, sedatives, rest treatment, thiamin administration); (c) prevention of an excessive accumulation of sodium in the heart muscle due to an increased action of the adrenal cortex (restriction of sodium intake).

On the basis of a multitude of facts, reported in the international literature, and of personal observations, the outstanding primary rôle of neuro-hormonal biochemical factors in the origin of myocardial anoxia and damage is stressed against the traditional mechanistic concepts.

TABLE I
Pathogenic Rôle of Cardiotoxic Adreno-Sympathogenic Effects in
Some Forms of Heart Disease

Type of Disease	Epinephrine-Sympathin in the Blood	Ekg. Changes of Anoxic (Epinephrine) Type	Special Adreno-Sympathogenic Clinical Features	Excessive Amounts of Epinephrine-Sympathin in the Heart Muscle	Myocardial Structural Changes Attributable to Toxic Epin.-Symp. Action	Probable Cause of Exaggerated Epinephrine-Sympathin Action upon the Heart
Angina pectoris on effort, etc.	Abnormal acute discharges on effort, etc.	Usually present during attacks, on exertion, etc.	Blood pressure elevation during attacks common	Usually present	Often present (where cor. sclerosis insignificant)	Excessive irritability of adreno-sympathetic neuro-secretory mechanism
Sudden death without morphological findings	?	?	Anginal pain, pulmonary edema preceding death	Present in 2 cases examined (and in all animals killed by epinephrine injection)	Occasionally present	Excessive acute adreno-sympathogenic discharges, often precipitated by emotions, strenuous exercise
Thyrotoxic heart	Normal	Occasionally present	Tachycardia, high pulse pressure	Not present (animals)	Frequently present	Abnormal sensitization of the heart to normal amounts of epinephrine-sympathin through excess thyroid hormone
Beri-beri heart	Increased (animals)	Usually present	"Pistol-shot pulse," exaggerated epinephrine sensitivity, pulmonary edema	Usually present (animals)	Usually present	Excessive adreno-sympathogenic neurosecretion, probably in connection with adrenal hyperplasia
"Hypertensive" heart (with or without hypert.)	Exaggerated acute discharges common, but otherwise normal level	Often present	Occasionally tachycardia, pulmonary edema. Blood pressure usually elevated	Usually present	Often present (where cor. sclerosis insignificant)	Potentialization of epin.-symp. effects on heart by cortical sterols (possibly through alteration of myocardial electrolyte balance); increased adreno-sympath. secretory irritability
Uremic heart	Regularly constantly increased	Usually present	Pulmonary edema common, occasionally tachycardia	Almost always present	Usually present	Accumulation of epinephrine-sympathin in the blood and heart, probably because of insufficient renal excretion

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CASE REPORTS

IMMEDIATE FATALITIES AFTER INTRAVENOUS MERCURIAL DIURETICS *

By ROBERT E. KAUFMAN, M.D., *New York, N.Y.*

SUDDEN deaths shortly after the intravenous injection of various mercurial diuretics, although rare, have been reported with increasing frequency in recent years. Reported instances¹⁻¹⁵ of fatalities within a few minutes after the injection, and apparently caused by it, now total 31 (table 1). Another case is added below. Deaths occurring many hours or days after the injection, even though there appears to be a definite relationship, are not included, since the mechanism is entirely different. In addition to the fatalities, there have been many, very severe reactions recorded,^{5, 12, 16} and undoubtedly many more that were never reported. A study of the descriptions of these cases shows that in most instances it was merely by the greatest good fortune that they were not fatal, so closely do they resemble the fatal ones. There have been reports of several cases in which the intravenous injection of the mercurial diuretic may have been the direct cause of death, but in which the time relations, moribund condition of the patient, and other factors leave room for doubt about the rôle of the mercurial.¹⁷⁻²¹

CASE REPORT

A 21 year old white female was admitted to the hospital July 12, 1946. She had been well up to one week before, when she developed nausea, vomiting, diarrhea; sudden weight gain of 20 pounds; and swelling of the legs, thighs, and face. About three years previously she had cessation of the menses for three months and a sudden gain in weight of 21 pounds; this added weight gradually disappeared spontaneously. She had scarlet fever as a child, but no rheumatic fever or any known heart or kidney disease.

Examination on admission showed marked edema of the legs, thighs, abdominal wall, face and eyelids. The blood pressure was 108 mm. Hg systolic and 70 mm. diastolic; and it was never elevated subsequently. The rest of the physical examination was entirely negative. Laboratory examinations were as follows: Urine: specific gravity 1.022; albumin 3 plus (3.6 grams per liter); sugar negative; microscopic: few hyaline and granular casts, occasional leukocyte, no red blood cells. Hemoglobin, red blood cell, white blood cell, and differential counts were all normal. Blood urea N, non-protein N, and uric acid determinations were normal; cholesterol was 577 mg. per 100 c.c.; serum proteins varied between 3.00 and 3.90 gm. per 100 c.c.; albumin 1.4 to 2.0; globulin 1.6 to 2.1. The basal metabolic rate on three occasions was minus 18, 11, and 17. Urine concentration test was normal.

The diagnosis was lipid nephrosis. During her six week stay in the hospital, she was treated at various times with the following: high-protein, low-salt diet; limited fluids; amino acids per os and intravenously; plasma and concentrated human

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From The Lenox Hill Hospital, New York, N. Y.

serum albumin; ammonium chloride; thyroid extract. In addition, she received Mercupurin intravenously seven times between July 25 and August 15 with no reaction. The first dose was 1 c.c. and all subsequent doses were 2 c.c. She left the hospital August 20, feeling somewhat better and down to her usual weight; but the serum proteins remained very low (albumin 1.4; globulin 1.6; total 3.0 gm. per 100 c.c.).

During the next three weeks she was at home, although not in bed. She continued thyroid extract 5 grains daily; and tried to take a high-protein, low-salt diet. She complained of anorexia, nausea, occasional vomiting and diarrhea, weakness, pallor, and dyspnea on exertion. On September 12 examination revealed a pulse of fair quality, regular rhythm, rate 88; a low blood pressure (90/50); marked pallor; moderate generalized edema; and a weight gain of five pounds since discharge three weeks before. She was given her eighth intravenous Mercupurin injection (2 c.c.), which was 28 days after the previous injection. It was given over a period of about 1 to 1½ minutes after having drawn back about 0.4 c.c. of blood.

Within 30 to 45 seconds after the end of the injection, the patient suddenly became even more pale, looked startled, was unable to talk, gasped a few times. The eyes rolled and the pupils dilated widely; the arms and legs jerked convulsively; and there was incontinence of feces. Soon respirations ceased and the pulse could not be obtained. At the onset of the reaction she was immediately given 1 c.c. epinephrine intramuscularly and artificial respiration, which was continued for 25 to 30 minutes. During this time she was given oxygen by mask, and caffeine sodium benzoate and more epinephrine by injection. Death occurred between 3½ and 4½ minutes after the end of the injection. Permission for an autopsy was not obtained.

DISCUSSION

In table 1 the pertinent data of the reported fatal cases in which death followed immediately after the injection of mercurial diuretics are listed. The number of unequivocal cases is 32, including the one reported above. All 32 deaths occurred after intravenous injection. None has ever been recorded following administration by any other route. A study of the table shows that the fatalities were caused by many different drugs: Mercupurin, Salyrgan, Neptal, Esidrone, Mersalyl. The majority followed the use of Mercupurin or Salyrgan, probably because they have been employed much more often than the others. Age and sex seem to play no rôle. The diagnoses were: congestive heart failure 16; nephritis 7; nephrotic stage of nephritis 4; nephrosis 4; unknown 1. From these diagnoses it does not appear that mercurial diuretics are more dangerous in one type of condition than in another, considering that the two commonest indications for their use are congestive heart failure and nephritis. The number of injections prior to the fatal one was most varied. Six deaths occurred with the first injection; eleven with the second, third or fourth; at the other extreme, some patients had had 42 or 100 or even 200 previous injections. The interval between the preceding injection and the fatal injection is apparently of no significance; it was frequently one to four days, but was occasionally several weeks or months. The quantity given was usually 2 c.c. in adults and 1 c.c. in children. It must not be assumed that the patients were moribund when they received the last injection, as many were ambulatory and apparently doing well.

Clinically the fatal reaction usually starts one to three minutes after completion of the intravenous injection. Frequently the patient cries out or gasps; cyanosis and pallor may be marked; substernal distress, dyspnea, orthopnea, ir-

TABLE I
Immediate Fatalities Following Mercurial Diuretics

Authors	Cases	Age	Sex	Diagnosis	Drug	No. Inj.	Days Since Last Inj.
Wolf and Bongiorno ¹	1	4	?	Nephritis	Salyrgan	5	?
Sundaram ²	1	10	M	Heart failure	Salyrgan	1	—
Cadbury ³	2a	21	F	Nephritis	Salyrgan	3	?
	b	5	M	Nephritis	Salyrgan	?	?
Greenwald and Jacobson ⁴	2a	2	M	Nephrotic state	Neptal	3	7
	b	3	M	Nephrosis	Neptal	3	3
Tyson ⁵	1	3	M	Nephrosis	Mercupurin	2	1
Vaughn ⁶	1	16	M	Heart failure	Mercupurin	1	—
Barker et al. ⁷	4a	59	M	Heart failure	Salyrgan	14	3 mos.
	b	48	M	Nephrotic state	Mercupurin	1	—
	c	64	F	Heart failure	Salyrgan	200	28
	d	64	F	Heart failure	Salyrgan	1	—
Brown et al. ⁸	4a	68	M	Heart failure	Mercupurin	13	?
	b	52	F	Heart failure	Mercupurin	24.	?
	c	48	F	Heart failure	Mercupurin	43	7
	d	60	F	Heart failure	Mercupurin	9	?
DeGraff and Nadler ⁹	1	60	M	Heart failure	Mercupurin	2	12
Evans and Perry ¹⁰	6a	15	M	Nephritis	Salyrgan	2	4
	b	51	F	Nephritis	Salyrgan	4	3
	c	5	M	Heart failure	Mersalyl	6	3
	d	47	F	Nephritis	Salyrgan	3	2
	e	57	M	Heart failure	Neptal	4	2
	f	7	M	Nephritis	Neptal	2	4 mos.
Richards and Moench ¹¹	1	59	F	?	Salyrgan	"many"	?
Wexler and Ellis ¹²	2a	24	F	Heart failure	Mercupurin	100	2
	b	27	F	Nephrosis	Mercupurin	14	?
Rennie ¹³	1	45	F	Nephrotic state	Neptal	7	23
Volini et al. ¹⁴	3a	20	M	Heart failure	Mercupurin	4	2
	b	68	M	Heart failure	Esidrone	6	4
	c	69	F	Heart failure	Esidrone	1	—
Murphy ¹⁵	1	27	F	Nephrotic state	Neptal	1	—
Author	1	22	F	Nephrosis	Mercupurin	8	28

regular and labored respirations are common; convulsions are frequent; dilatation of the pupils is occasionally seen. There may be palpitation, tachycardia, fall in blood pressure, and irregularity of the cardiac rhythm; coma, cessation of respiration and of heart beat then occur. There have been numerous cases in which many of the above symptoms and signs were present and in which a fatal outcome seemed certain, but in which recovery occurred without specific therapy.^{5, 12, 16} Another group of cases is that in which symptoms, sometimes exceedingly severe or even fatal, are due to salt depletion and upset of the

electrolyte balance caused by the marked diuresis. These symptoms usually start from 6 to 12 hours after the injection.^{16, 21-28} Some minor or severe reactions are undoubtedly on an allergic basis.²⁴ Finally, some cases, including a few fatal ones, are obviously due to mercury poisoning in the usual sense, affecting the alimentary tract or the kidneys.

The mechanism of sudden, immediate fatalities following the intravenous administration of mercurial diuretics has been clearly elucidated by several groups of investigators working with dogs and cats²⁵⁻³⁰ and by some clinicians in humans.^{14, 16} Death is caused by a direct action of the mercury in these drugs on the cardiac musculature. An early manifestation is a change in intraventricular conduction, while the terminal effect is usually ventricular fibrillation. In 1922 Salant and Kleitman²⁵ demonstrated ventricular fibrillation in dogs after the intravenous administration of inorganic mercury salts or Mercurochrome. A few years later Jackson²⁶ showed that the intravenous injection of Salyrgan in dogs produced death from ventricular fibrillation. Chastain²⁷ gave Esidrone, another organic mercury compound with theophylline, intravenously to dogs and produced death from ventricular flutter and fibrillation. DeGraff and Lehman²⁸ obtained the same results in cats following intravenous administration of Mercupurin. Pines, Sanabria, and Arriens²⁹ gave Esidrone intravenously to dogs, and the electrocardiograms showed: "Changes of T-waves, intraventricular and auriculo-ventricular conduction disturbances, diminution of frequency of impulse formation in the S-A node, ventricular paroxysmal tachycardia, chaotic heart action, ventricular fibrillation, and death." Chapman and Shaffer³⁰ recently corroborated the results of previous investigators. They found, in a large number of dogs in whom they took electrocardiographic tracings, that both Mercupurin and Salyrgan injected intravenously caused death from ventricular fibrillation, whereas Mercurhydrin caused death from ventricular asystole. They were unable to offer any explanation for this difference.

Volini, Levitt, and Martin¹⁴ were able to get electrocardiographic tracings on two patients from the time they received the mercurial diuretic intravenously until they died very shortly after the injection. Both showed the development of ventricular fibrillation; and one "showed changes very similar to the experimental electrocardiogram in anesthetized dogs; i.e., changes in the ST interval, intraventricular conduction deformity and changes in the T wave." Ben-Asher¹⁶ had one patient in whom electrocardiographic evidence of the cause of a severe, immediate reaction was obtained. "An electrocardiogram taken during the reaction showed changes in the P wave, ST segment, and the T wave, followed by ventricular premature systoles and paroxysmal ventricular tachycardia. The patient recovered, and the electrocardiogram returned to normal sinus rhythm." The reaction followed immediately after the intravenous injection of 2 c.c. Mercupurin, and consisted of substernal distress, pallor, labored respirations, rapid and irregular pulse. Although this patient recovered spontaneously, it is apparent that the reaction was very similar to the fatal ones. The evidence, experimental and clinical, of the toxic effect of mercury on the heart muscle, occasionally causing ventricular fibrillation and death, seems definite and conclusive.

With the knowledge of the cause of the sudden deaths sometimes seen following administration of mercurial diuretics intravenously, it might be possible

to make suggestions for avoiding these unfortunate fatalities. Some have suggested giving the mercurial diuretics orally³¹ or rectally. These routes are not always sufficiently effective and occasionally cause local irritation. Modell, Go' and Clarke³² have recently shown that the average diuretic response with 1 c.c. or 2 c.c. intravenously or 2 c.c. intramuscularly of either Mercupurin or Mercuhydrin is practically identical (4.0 to 4.4 pounds weight loss per injection). Strangely enough, 0.5 c.c. intravenously of either drug gave an even greater average diuresis (6.5 to 7.5 pounds weight loss per injection). Similar results have been obtained by several other investigators.³³⁻³⁵ Finkelstein, Smyth, and Yonkman^{31, 35} found Mercuhydrin as effective intramuscularly as intravenously. Mercuhydrin appears to be less irritating than Mercupurin by intramuscular injection.³² In choosing the route of administration, it should be remembered that all the mercurial diuretics cause severe pain if a small amount gets outside the vein during an intravenous injection.

The diuretic response is usually considerably more marked with the mercurials when ammonium chloride in adequate dosage has been previously administered.^{31, 35} Therefore a small dose of the mercurial given after large amounts of ammonium chloride will give better results and will probably be safer than large doses without prior acidification. Another point to be stressed is that there seems to be "a definite advantage to the administration of smaller doses [of a mercurial diuretic] repeated at short intervals over larger doses once a week; two small doses appear to give more diuresis than one large one."³⁶

Ben-Asher¹⁶ stated that "reactions may be avoided by intermittent injection—0.1 c.c. intravenously every 15 seconds." In his series, "in eight cases the reaction occurred immediately after the injection. In seven cases reactions did not occur when the [subsequent] injections were given slowly and intermittently. In one case a reaction did not occur when the [subsequent] injection was preceded by 1.0 gram sodium thiosulfate intravenously." It is not possible, of course, to be sure that the absence of further reactions in this group of patients was due to the "intermittent" method of administration; but with this method if a patient starts having a reaction, the injection can be terminated immediately. Another suggestion that has been made is that if any sort of reaction occurs, a change be made to a different mercurial for future injections. Gold and his co-workers^{24, 32} report three cases in which a shift to another compound enabled them to continue with mercurial diuretics without further reactions.

Pines, Sanabria, and Arriens²⁹ state that "the addition of small quantities of magnesium sulphate (0.5 c.c. of a 20 per cent solution) prevents ventricular fibrillation and death [in dogs] even if doses seven times higher than normal lethal doses are used. Such amounts increase the diuretic response, are entirely safe, and mix with the mercurial diuretics without forming any precipitate. It is suggested that small quantities of magnesium sulphate be incorporated into mercurial diuretics in order to prevent fatal reactions resulting sometimes from the intravenous injection of these drugs." Chapman and Shaffer³⁰ found that ascorbic acid given with Mercuhydrin intravenously "increases the average minimum lethal dose over 50 per cent and gives up to 50 per cent greater diuresis." They believe that "Mercuhydrin (2 c.c.) with ascorbic acid (500 mg.) [in the same syringe] is the least cardiotoxic and the most potent intravenous diuretic."

Some suggestions for trying to avoid sudden, immediate fatalities and near-fatalities are as follows:

1. Use the intramuscular route whenever satisfactory diuresis is thereby obtained. For this, Mercurhydrin appears to be the best drug, since it is effective and at the same time the least irritating. As pointed out previously, no death has been reported thus far by any route other than the intravenous. This is undoubtedly due in part to the fact that the intravenous is the most common method of administration; but on theoretical grounds this should be the most dangerous route because death is caused by the sudden action of the mercurial on the cardiac musculature.

2. Use the oral or rectal route for maintenance doses when sufficient diuresis is thus obtained without gastric or rectal irritation.

3. Use the intravenous route when the above methods do not suffice or when rapid and certain diuresis is imperative. One should employ the smallest efficacious dose, rarely more than 1 c.c. Although the statement is frequently made that the size of the dose does not influence the fatality rate, it seems logical to give the smallest amount that produces a good therapeutic effect.

4. Give small amounts for the first three intravenous injections, since six of the 32 deaths listed in the table occurred with the first injection and eight more with the second or third. The first injection should not exceed 0.5 c.c. and the next two 1 c.c. unless the condition of the patient is desperate and the added risk of larger initial amounts is justified.

5. Administer acidifying salts, such as ammonium chloride 6 to 12 gm. daily, for at least 48 hours prior to each injection. Acidifying salts often induce diuresis, but not so satisfactorily or reliably as when followed by a mercurial.⁸⁷ By combining the action of the acidifying compounds with that of the mercurials, one can give less of the latter and also may get satisfactory diuresis by some route other than the intravenous.

6. Employ slow, intermittent injection, 0.1 c.c. every 15 seconds, either routinely or at least for the first three intravenous injections and in those patients exhibiting any reaction to previous injections. Although some authors^{10, 28} state that slow injection does not reduce the incidence of these sudden deaths, any measure that might reduce the number of these unfortunate accidents is worthwhile.

7. Change to another mercurial diuretic in individuals exhibiting any sort of allergic reaction.

8. Administer mercurial diuretics only when clearly indicated, and "occurrence of danger signals warrants complete reevaluation of the therapeutic regimen".¹² The warning reactions consist of any of the following: rash, urticaria, angioneurotic edema, chills, fever, pallor, cyanosis, substernal distress, palpitation, tachycardia, fall in blood pressure, cardiac arrhythmias, dyspnea, orthopnea, shock, collapse, convulsions.

With respect to patients who have had a sudden, immediate and near-fatal reaction, my opinion is that they should never again have intravenous injections of any mercurial, even though Ben-Asher¹⁶ had some patients who had no further reactions when given intermittent injections or prior sodium thiosulfate. Most of his patients who had a severe, immediate reaction died six to 10 weeks thereafter. He believes that "the markedly diseased heart muscle is particularly sensitive to the mercurial diuretics." This seems a good reason for giving these patients no further intravenous injections of these compounds.

The suggestion¹⁶ of administering sodium thiosulfate intravenously prior to

each intravenous injection of a mercurial seems impractical. However, the suggestion of incorporating a small quantity of magnesium sulfate²⁹ or of ascorbic acid³⁰ into mercurial diuretics for intravenous use, based on the experimental observation that the addition tends to prevent ventricular fibrillation or asystole and death, seems logical, safe, and simple. If such a "modified" mercurial diuretic becomes available commercially, it would probably be safer than any now obtainable.

There is no evidence that death is more likely to occur when drugs such as ammonium chloride, phenobarbital, or digitalis are given with the mercurial diuretic¹⁰; and a relatively good state of health is no protection against a fatal reaction.¹² The recoveries in the immediate, near-fatal reactions appear to be spontaneous. There is at present no known specific treatment for the usual type of severe reaction. The doctor will try artificial respiration and epinephrine, and he will sweat and pray; but recovery will depend on the ability of the heart muscle to recover from the ventricular arrhythmia caused by the mercurial.

SUMMARY

1. One fatality following immediately after the intravenous administration of a mercurial diuretic is added to the 31 previously reported cases.

2. The incidence of these sudden deaths is apparently not influenced by the variety of mercurial compound employed, by the patient's age or sex, by the disease causing the edema, by the number of previous injections or the interval between them, or by previous medication. However, the size of the dose and the speed of the injection may be of some importance.

3. Death is caused by the direct action of the mercury, administered intravenously, on the cardiac musculature, causing changes in the intraventricular conduction and terminally ventricular fibrillation.

4. The clinical manifestations of the fatal and near-fatal reactions are described, and suggestions are given for attempting to prevent fatalities.

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MEDIASTINAL MASS SIMULATING ENLARGED HEART, INTRACARDIAC CATHETERIZATION IN DIAGNOSIS *

By LEONARD CARL AKMAN, M.D., *Baltimore, Maryland*

ANTERIOR mediastinal tumors are relatively rare. Correct recognition, however, is essential in determining the wisest course and method of therapy. To date about 300 cases have been reported, yet each presents a different picture, a new challenge to diagnosis. The signs, symptoms, and clinical course are so varied as to preclude any generalization. No single diagnostic measure can give even a minimum of the necessary information; all the diagnostic measures at one's disposal must be utilized. The object is to discover the nature of the tumor, to determine its relationship to lung, chest wall, and mediastinum, and to visualize its point of attachment.

The case herein reviewed posed a problem unusual in the literature of these bizarre tumors. An initial chest plate revealed what appeared to be the configuration of a heart enlarged to the left and to the right; the border was uninterrupted, the shadow homogeneous in density. Under fluoroscopy there were bilateral pulsations. In making a diagnosis of an extra-cardiac mass a number of measures were used, including the introduction of a radio-opaque catheter into the heart for the purpose of helping outline its borders.

Catheters have been introduced into the heart to study hemodynamics or to inject radio-opaque liquids, but the literature reveals no report of its use as a probe in exploring the accessible parts of the cardiovascular system. Unique information may be obtained by the procedure. It is presented along with an unusual case in which it proved helpful and in which it was evaluated with other procedures.

CASE REPORT

History: D. C., a 15 year old white girl, was admitted to Sinai Hospital July 3, 1945, because of recurrent attacks of chest pain.

She had been well until six months before her admission when she awoke one morning with pain in the right upper back, medial to the spine of the scapula and in the shoulder. The pain was described as a "soreness" decreasing slightly on bringing the shoulder forward. It lasted one day.

There was no recurrence until four months before admission, when she again awoke with a "soreness" over the right scapula region, severe enough to keep her home from school and lasting two days before subsiding without therapy.

Ten days prior to admission she suffered a third attack of pain, this time accompanied by fever. Fever and malaise appeared first in the afternoon, and were soon followed by the characteristic pain which radiated, this time, to the right flank. By evening the pain was worse. When her physician was called he found her temperature to be 104°. There had been no chills, cough, or sputum. The patient was put on sulfadiazine and within 36 hours the pain and fever were gone.

One week later she was referred to Sinai Hospital for study.

Family History: Negative.

Past History: She was not a "blue baby." There were no signs or symptoms referable to the cardio-respiratory system until her present illness, except at eight

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From the Medical Service of the Sinai Hospital, Baltimore.

years of age, when the patient developed a persistent cough lasting a few weeks. She was x-rayed at that time; the findings were diffuse bilateral peribronchial thickening. No consolidation or fluid was noted. The impression was diffuse bronchitis due to recent infection. Further mention is not made of the mediastinal configuration. Unfortunately, the plate was discarded by the roentgenologist.

Physical Examination: On admission the patient was afebrile and asymptomatic. The temperature was 99° (R), pulse 80, respirations 22, blood pressure 110 mm. Hg systolic, 70 mm. Hg diastolic.

The patient, a well-developed, well-nourished girl, appeared comfortable, not dyspneic or orthopneic. The lips were slightly cyanotic. There was no venous distention and no venous pattern. The positive findings were confined to the chest which, on inspection, presented no asymmetry or lag.

Heart: There was no visible apical beat; to palpation, no heave, shock, or thrill; but on percussion the cardiac outline was enlarged 8.5 cm. to the left, and curved out sharply to the right at the level of the second interspace for a distance of 6.5 cm.

The sounds were not remarkable, being regular and of good quality. There was a normal third sound at the apex, and no murmurs were heard. P₂ was split and slightly accentuated. P₂ was louder than A₂.

Lungs: Posteriorly on the right, there were impairment to percussion and diminished breath sounds along the lower two-thirds of the chest near the vertebral column. Otherwise the physical examination was negative.

Laboratory Data: Red blood cells 4.5 million, hemoglobin 100 per cent, white blood cells 8,000 (normal differential), sedimentation rate varied between 30 mm. and 46 mm. per hour (Wintrobe), hematocrit 40 mm., urine negative.

Chemistries (blood): Urea 21 mg. per cent, sugar 85 mg. per cent, P—3 mg. per cent, Ca—10 mg. per cent, total protein 7.4 gm. per cent, alkaline phosphatase 2.8 Bodansky units, cholesterol 196 mg. per cent.

Venous pressure 9 cm. of water. Circulation time, arm to tongue (decholin) 12 seconds, arm to lung (ether), 5 seconds.

Electrocardiogram: Normal tracing.

Roentgenological Studies: Chest plates—antero-posterior and lateral teleroentgenograms revealed the cardiac shadow enlarged, especially to the right (figures 1 and 2).

Fluoroscopy: The pulsations of both sides of the heart were normal; there was "notching" at the upper border of the right side.

Barium swallow revealed the esophagus to be in normal position and without constriction.

Bronchogram: Normal bronchial tree (figure 3).

At this stage the peculiar mediastinal shadow presented the problem of differentiation between the presence of an extra-cardiac mass and cardiac enlargement. It was decided that the answer might be obtained by passing a catheter as a probe into the right heart. If the catheter approached the right border of the shadow, we could assume that it was part of the heart.

Intracardiac Catheterization: The patient was moderately sedated prior to this procedure, which was carried out in the fluoroscopy room. Under aseptic technic and local anesthesia, the median basilic vein of the right arm was surgically exposed in the antecubital fossa. Two silk ligatures were passed under the vein and the distal one tied. The proximal ligature was used to steady the vessel as a small transverse nick was made and a No. 8 ureteral catheter inserted.

The catheter had previously been connected to a saline infusion set through which the fluid was allowed to run at about two drops a second. The catheter was pushed up easily and rapidly toward the axilla without any discomfort to the patient. Under

the fluoroscope the catheter was further introduced until the tip passed down into the right auricle.

The tendency of the catheter to straighten in the heart made it impossible to bring it over to the right border in spite of manipulation and twisting; rather, it tended to go over to the opposite side from its place of insertion.

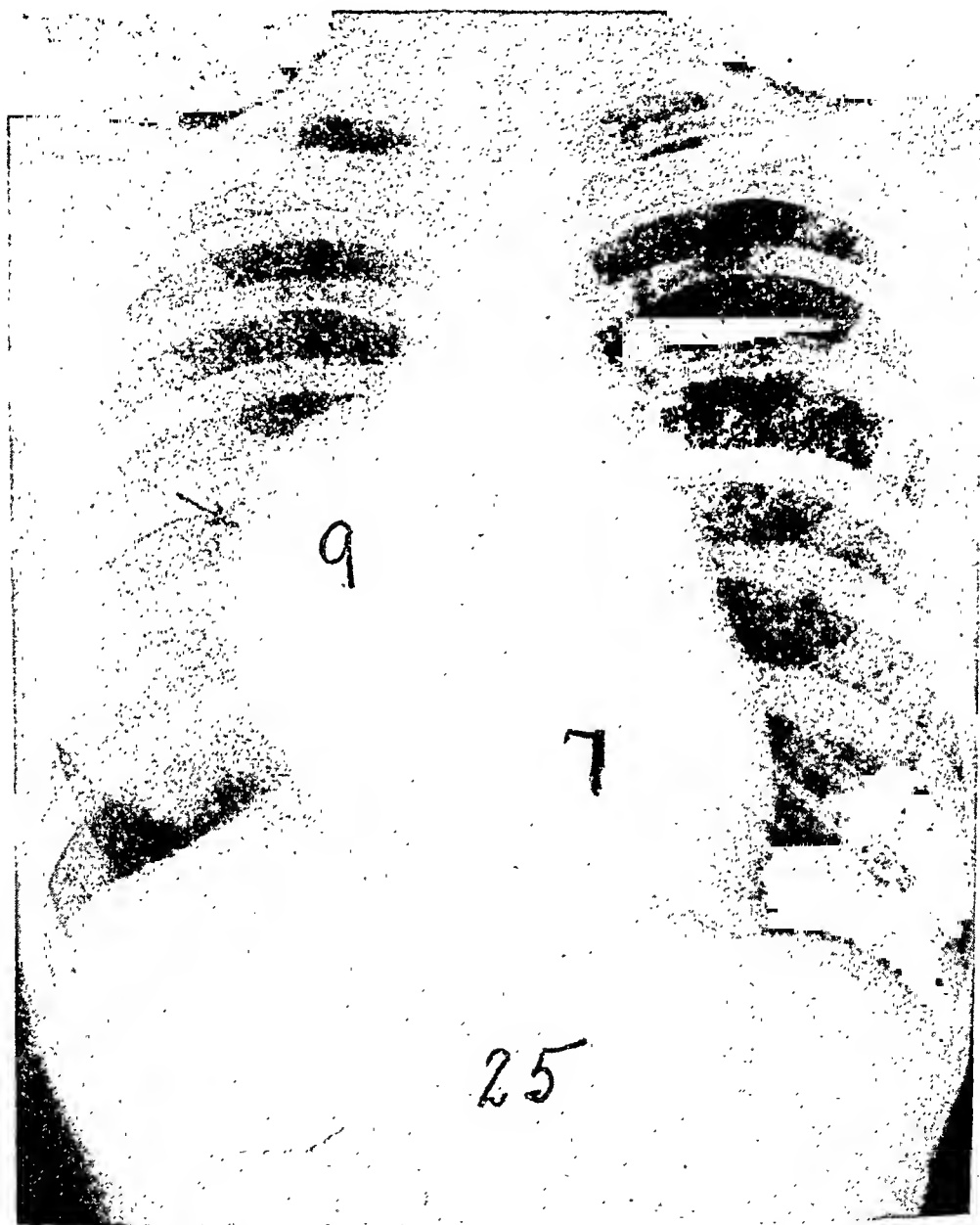


FIG. 1. Antero-posterior view.

Not only did the catheter fail to approach the right border, but it did not seem to meet with any obstruction in the auricle. The procedure added little to our knowledge. We concluded that the purpose would better be accomplished if the catheter were passed from the opposite side.

A few days later the procedure was repeated using the left arm. As anticipated, the tendency of the flexible catheter to straighten caused it to hug the right border of the heart. By repeated passage, the catheter outlined a bulge in the wall of the



FIG. 2. Right lateral view.

right auricle. The outline of the bulge was continuous with the outer border of the mediastinal shadow. It was evident that a mass was impinging on the right auricle (figure 4).

Pneumothorax: A right pneumothorax was done in anticipation of surgery and as a further diagnostic measure. This procedure was even more revealing than intracardiac catheterization.

On x-ray, part of the true right border of the heart could be seen extending below the border of a mass. Under fluoroscopy, one could now differentiate the



FIG. 3. Bronchogram, antero-posterior.

active pulsations of this small part of the heart from the pulsations transmitted to the mass. It was also seen that the mass was suspended by a pedicle from a point above the right auricle (figure 5).

Course in Hospital: Aside from the formation of small thrombi in both median basilic veins where they were incised, the patient suffered no ill effects from the introduction of the catheters.

At operation, a globular dermoid cyst about the size of a large orange was found. The cyst was adherent to the pericardium and was connected to a point just above the right auricle. The mass was successfully removed through an incision in the

fourth right interspace anteriorly. As expected, the incision brought the surgeon* down on the point of attachment. The pedicle was severed after the rest of the tumor was carefully separated from the mediastinum.

The patient had a smooth post-operative course. Figure 6 is the chest plate taken before discharge, revealing the yet incompletely expanded right lung.

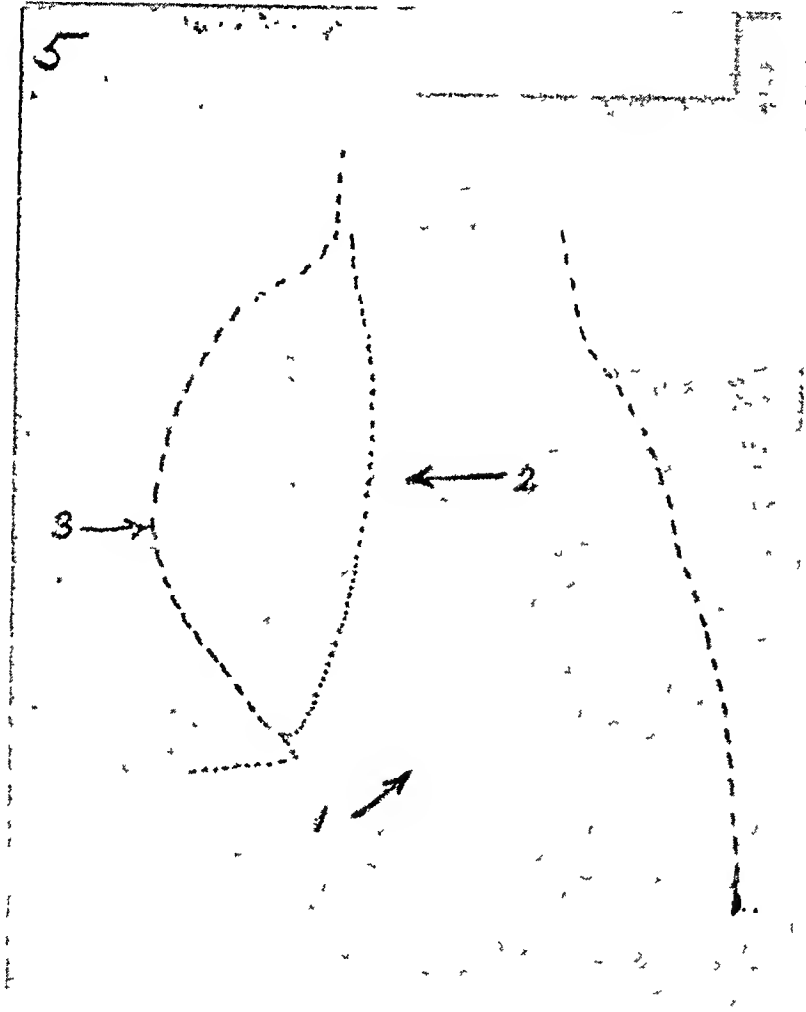


FIG 4 Spot film showing the catheter circumscribing the bulge produced by the mass impinging on the right auricle (1 catheter; 2 outline of mass; 3 mass).

DISCUSSION

Anterior mediastinal tumors are rarely mistaken for or confused with abnormal cardiac shadows on x-ray. The mediastinal outline here was highly suggestive of a congenitally malformed heart, especially since large septal defects or pulmonary valvular disease may produce no murmurs and but few symptoms. Pericardial cyst, or so-called inflammatory pericardial diverticulum, could also have produced such a shadow.

* Dr. Wm. F. Rienhoff, Jr., Staff Consultant Surgeon

Both procedures used ruled out cardiac enlargement as explaining the entire mediastinal shadow. Intracardiac catheterization demonstrated the presence of a mass displacing the heart, but not until an artificial pneumothorax was produced were we able to visualize both the tumor and its pedicle as being separate and

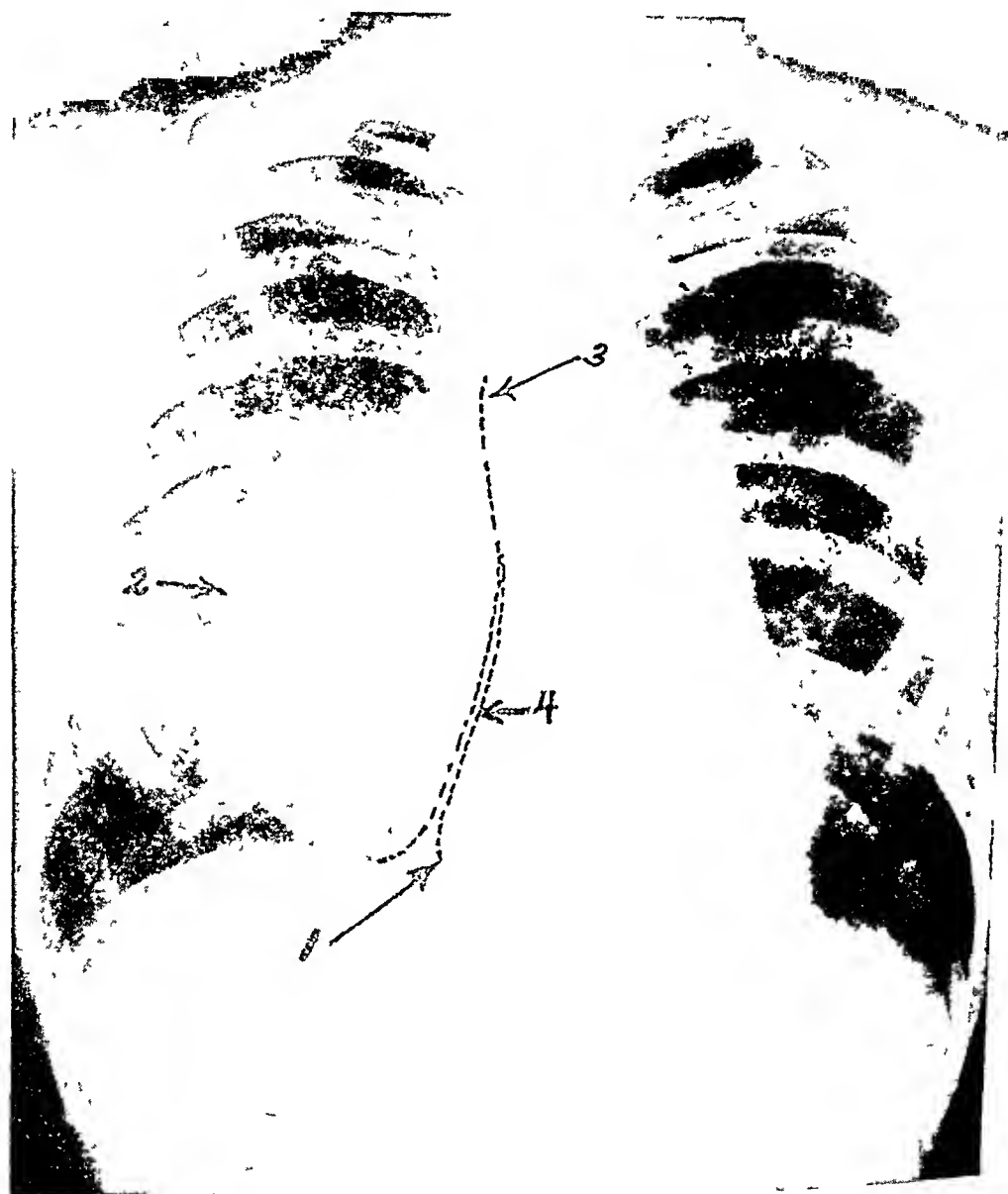


FIG. 5. Diagnostic pneumothorax, antero-posterior view (1 right border of heart, 2 mass; 3 pedicle; 4 line of decreased density seen more clearly under fluoroscopy). This procedure allowed the mass to swing away from the auricle. Under fluoroscopy, one could see the active pulsations of the heart, especially in that part of the border extending below the mass.

distinct from the heart. Visualization of the pedicle was particularly important to the surgeon. With the information derived from the pneumothorax, the diagnosis of dermoid cyst or teratoma was made before operation with a reasonable degree of certainty.

Had artificial pneumothorax preceded the intracardiac catheterization it would have obviated the need of the latter. But past experience has not always found artificial pneumothorax as conclusive as the evidence it presented here. The information disclosed by intracardiac catheterization is unique, and it is

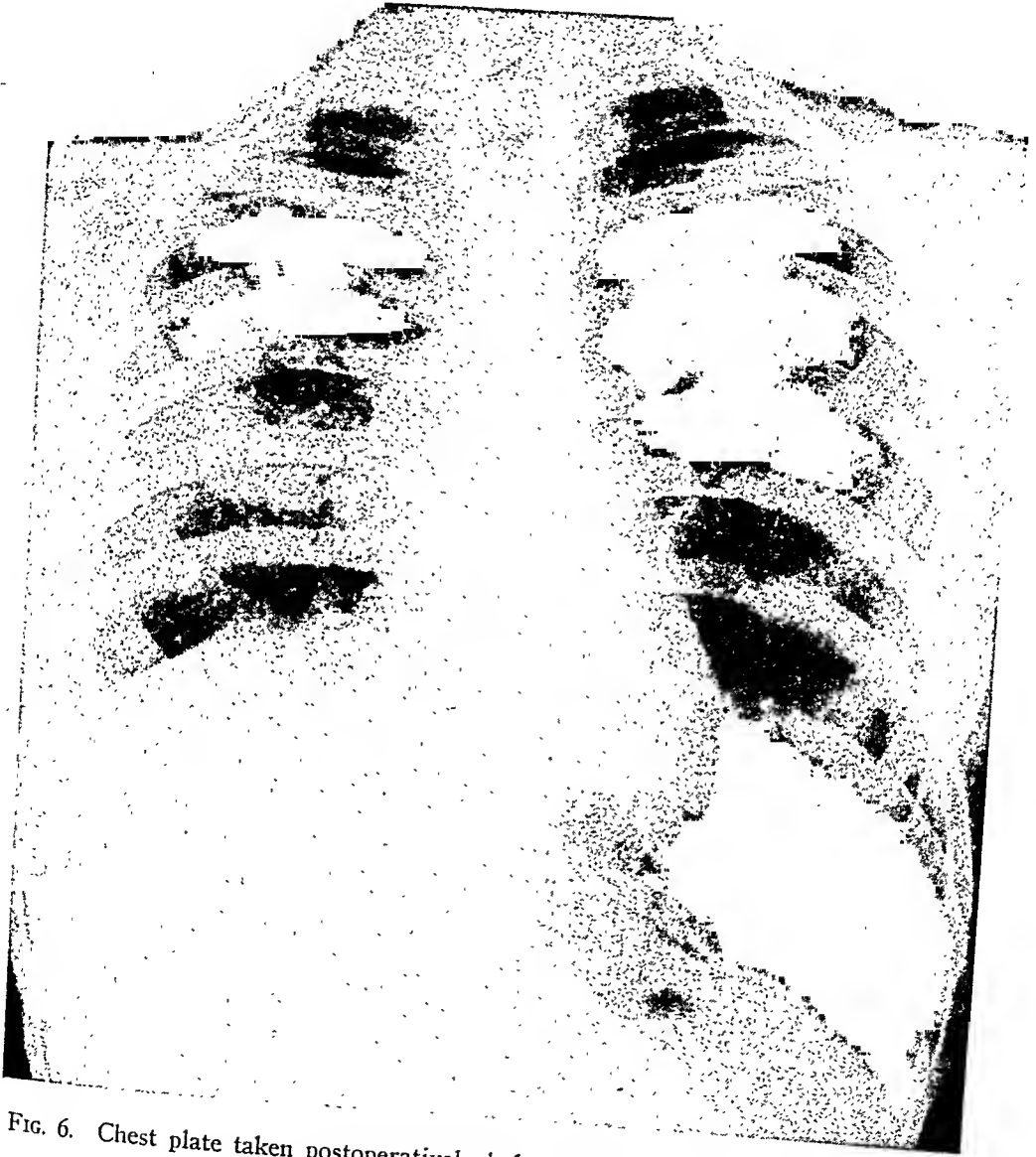


FIG. 6. Chest plate taken postoperatively before discharge. The right lung is not yet completely aerated.

likely that in certain cases it may yield essential information. It is offered as another procedure to be added to the armamentarium of the diagnostician.

Intracardiac catheterization is not so new that it need be considered a radical procedure. The clinical experience with its use is already extensive. Experiments have been reported in which it has been used in hundreds of individuals with but minor discomfort or reaction. We may consider it a relatively safe procedure when properly done, and to be used without hesitation when indicated.

Forssman⁸ reported introducing a catheter into the right atrium in 1929. Conte and Costa⁸ in 1933, following studies carried out first on animals, then on man, devised a method of visualizing the pulmonary vessels by injecting radio-opaque liquid through bilateral catheters introduced simultaneously into the right auricle. These writers refer to the work of Ravina and his collaborators, who had made extensive pathologic studies on animals in which intracardiac catheterization was done. Ravina observed no lesions of the endothelium. (Conte and Costa themselves have also carried out the procedure on a case of mitral stenosis and pulmonary congestion.)

Cournand^{4, 5, 6} and his workers have described a technic similar to that used in this case. In hundreds of intracardiac catheterizations, they observed no unfavorable complications other than thrombosis at the site of insertion of the catheter. Occasionally there was a slight rise in respiratory rate or a small degree of bradycardia. In some cases the catheter was left in as long as 24 hours. Pathological examination in patients later dying of other causes revealed no evidence of damage to the endocardium or valve leaflets. The procedure in one series of 31 attempts was unsuccessful in seven only because of obstruction along the course of the vessel or inability to make the catheter follow the desired course. Their experience vouches for the safety and simplicity of the procedure.

SUMMARY

1. A case is presented in which an anterior mediastinal tumor simulating an enlarged heart was successfully removed following correct preoperative diagnosis of the type of tumor and its point of attachment.

2. The use of intracardiac catheterization as a probe is discussed and compared with the value of diagnostic pneumothorax in this case.

Acknowledgment. The writer is happy to express his thanks to Dr. Marcus Ostro, Chief of the Department of X-Ray, and to his staff for their complete cooperation; and to Dr. Elliot Newman, a physician of the Johns Hopkins Hospital, who initiated the writer into the technic of introducing the catheter.

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TOXIC PSYCHOSIS RESULTING FROM PENICILLIN *

By CARL L. KLINE, M.D., and LARUE S. HIGHSMITH, M.D., *Columbia, Missouri*

ALTHOUGH a variety of allergic reactions have been described following the therapeutic use of penicillin,¹ no instance of toxic psychosis resulting from this drug has, to our knowledge, previously been reported.

CASE REPORT

The patient was an 18 year old white, single, female college student. She first received penicillin for an upper respiratory illness on March 13, 1947, at which time she received a total of 480,000 units intramuscularly in 36 hours without any type of reaction. On March 18, 1947, she was readmitted to the school infirmary with an otitis media, and penicillin was again prescribed. She received a total of 420,000 units intramuscularly and 3,800,000 units orally over a period of 10 days and was discharged on March 27, 1947. On March 29 she was readmitted with a temperature of 101°, generalized urticaria, and arthralgia. Her fingers, knees, and ankles were swollen, red, painful, and tender. There was no evidence of residual otitis media, and neurological examination was negative. Her sedimentation rate was 16 mm. in 60 minutes (Cutler), her urine negative, and her blood count as follows: red blood cells 4,550,000, hemoglobin 13.4 gm., white blood cells 19,600, polymorphonuclears 91 per cent, lymphocytes 5 per cent, monocytes 4 per cent.

She was placed on 100 mg. pyribenzamine every four hours (three doses a day). On her second hospital day she received one gram of novocaine in 500 c.c. of 5 per cent glucose in saline, and the severe pain from her arthralgia subsided within 30 minutes. On April 4, her fourth hospital day, she became extremely restless, picked at the covers constantly, and complained of hearing voices. She became suspicious of everything and everyone. She accused one of the doctors of having just talked with her father on the telephone and said that she had heard his voice clearly. She heard voices coming through the window and from an adjacent private room and was observed responding to them. In retrospect, it was recalled that she had been unduly suspicious of the preparation for giving her the novocaine infusion two days before and had expressed the idea that a poison was being administered.

When the psychotic manifestations appeared, the pyribenzamine was stopped. The giant hives, which had begun to subside, immediately exacerbated, and her mental symptoms became more pronounced. Pyribenzamine was again started the following day, and two days later the mental symptoms had subsided and did not return. The urticaria had also nearly completely subsided at that time. Two days later her temperature had returned to normal, and from then on the course was uneventful.

* Received for publication June 23, 1947.

It seems likely that, with such a severe, generalized urticaria and arthralgia, resulting from penicillin sensitivity, there were edematous lesions in her brain which produced the psychotic manifestations. When the urticaria and arthralgia subsided under pyribenzamine therapy, the mental symptoms also subsided. The facts that the urticaria and mental symptoms exacerbated when pyribenzamine was stopped for a day and subsided after it was resumed rule out that drug as a cause for psychosis.

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EDITORIAL

HEPATITIS IN INFECTIOUS MONONUCLEOSIS

INFECTIOUS mononucleosis in the past has signified to many physicians a mild infectious disease primarily affecting the nasopharynx and distinguishable from ordinary infections of the upper respiratory passages by striking enlargement of the lymph nodes, the appearance in the blood of large numbers of lymphocytes of characteristic bizarre type, and the development during convalescence of heterophile agglutinins for sheep red blood cells. It was early recognized, however, that many cases differ markedly in their clinical features from this classical type and that in individual cases there may be evidence of involvement of many different organs and tissues. Among these may be mentioned primary enlargement of the axillary or inguinal nodes or of the deep lymph nodes of the mediastinum or mesentery, cutaneous eruptions of various sorts including purpura and other hemorrhagic phenomena, areas of interstitial pneumonia, myocardial injury indicated by electrocardiographic abnormalities, nephritis, and meningitis or meningeal irritation. A "visceral" or typhoidal type of infection without any peripheral local manifestations has also been recognized. The infection, therefore, is a truly generalized one.

Jaundice has been recognized as an occasional manifestation of infectious mononucleosis since the report of Mackey and Wakefield in 1926.¹ The incidence of jaundice has varied greatly in different series of cases reported from about 1 to 12 per cent. In the large series (556 cases) reported by Wechsler et al.² there were 36 (5 per cent) with jaundice. This probably depends in part upon the severity of the cases observed, since jaundice is uncommon in the very mild cases which appear to be relatively frequent but rarely recognized except in systematic studies during epidemics.

The jaundice at first was attributed to pressure on the bile ducts by enlarged abdominal lymph nodes, although no direct proof of such a mechanism was ever advanced. Later studies, however, indicate that the jaundice is the result of an acute hepatitis. Such studies have been handicapped by the rarity with which cases of this disease have come to autopsy. Punch biopsies of the liver, however, have been carried out in cases of infectious mononucleosis complicated by jaundice by Kilham and Steigman³ in one case and by Bang and Wanscher⁴ in four cases. All these showed focal areas of hepatitis, located chiefly in the portal areas, with cloudy swelling and

¹ MACKEY, R. D., and WAKEFIELD, E. G.: The occurrence of abnormal leukocytes in the blood of a patient with jaundice (infectious mononucleosis-glandular fever), *Ann. Clin. Med.*, 1926, iv, 727.

² WECHSLER, H. F., ROSENBLUM, A. H., and SILLS, C. T.: Infectious mononucleosis: report of an epidemic in an army camp, *Ann. Int. Med.*, 1946, xxv, 113-133, and 236-265.

³ KILHAM, L., and STEIGMAN, A. J.: Infectious mononucleosis, *Lancet*, 1942, ii, 452-454.

⁴ BANG, J., and WANSCHER, O.: The histopathology of the liver in infectious mononucleosis complicated by jaundice, *Acta med. Scandinav.*, 1945, cxx, 437-446.

vacuolization of the hepatic cells, focal necroses and infiltration with mononuclear cells, resembling the lesions seen in infectious hepatitis.

This conclusion receives support from studies of liver function in these cases. In Wechsler's series² of jaundiced cases, for example, the cephalin-cholesterol flocculation test was positive in 23 of 25 cases tested. In 13 cases in which satisfactory bromsulfalein retention tests were carried out, there was a marked retention in 10 and lesser degrees of retention in three, carried out late in the disease.

Enlargement of the liver demonstrable by palpation is relatively common. It was present in 12 per cent of Bernstein's series⁵ and in 17 per cent of Wechsler's. It occurs more frequently than jaundice, but it is not demonstrable in all jaundiced patients. Although the enlargement is usually slight, it may be marked and accompanied by tenderness.

Examination of the tissue of the liver of patients who were not jaundiced has been made in several instances. Van Beck and Haex⁶ and Davis et al.⁷ examined tissue obtained by punch biopsies. Autopsies have been obtained on several patients who died from spontaneous rupture of the spleen (e.g., Ziegler⁸ and Fisher⁹), which appears to be the most frequent direct cause of death in this disease. Ricker et al.¹⁰ reported two cases in which death was caused by extensive involvement of the central nervous system with the clinical manifestations of the Guillain-Barré syndrome. In all of the cases mentioned the liver showed histological evidence of a focal hepatitis with the accumulations of mononuclear cells in the portal areas and often focal necrosis and disappearance of liver cells. These were essentially identical with those seen in jaundiced patients and resembled those described in infectious hepatitis.

Such observations stimulated clinical studies of patients with infectious mononucleosis to determine the frequency of hepatitis by utilizing the usual tests of liver function. Cohn and Lidman¹¹ examined 15 consecutive cases without jaundice, in which the diagnosis was positively established. In all cases impairment of liver function was demonstrated by two or more tests. The thymol turbidity test was most consistently positive, but bromsulfalein retention was also demonstrated, and an increase in alkaline phosphatase was found in 7 of 8 cases tested. Serial studies showed that the function

⁵ BERNSTEIN, A.: Infectious mononucleosis, *Medicine*, 1940, xix, 85-159.

⁶ VAN BECK, S. I., and HAEX, A. J.: *Aspiration biopsy of the liver in infectious mononucleosis and in Besnier-Boeck-Schaumann's disease*, *Acta med. Scandinav.*, 1943, cxiii, 125.

⁷ DAVIS, J. S., et al.: Rupture of the spleen in infectious mononucleosis, *Lancet*, 1945, ii, 72-73.

⁸ ZIEGLER, E. E.: Infectious mononucleosis; report of a fatal case with autopsy, *Arch. Path.*, 1944, xxxvii, 196-261.

⁹ FISHER, J. H.: Visceral lesions of acute infectious mononucleosis: a report of two cases with fatal spontaneous rupture of the spleen, *Am. Jr. Path.*, 1946, xlii, 651.

¹⁰ RICKER, W., et al.: The association of the Guillain-Barré syndrome with infectious mononucleosis, *Blood*, 1947, ii, 217-226.

¹¹ COHN, C., and LIDMAN, B. L.: Hepatitis without jaundice in infectious mononucleosis, *Jr. Clin. Invest.*, 1946, xxv, 145-151.

gradually reverted to normal during convalescence. Carter and MacLagan¹² found the thymol turbidity test abnormal in 58 per cent of 19 cases.

DeMarsh and Alt¹³ found some evidence of impaired liver function in all of 19 cases studied. The cephalin-cholesterol flocculation test was positive in 15 of 18 cases, and retention of bromsulfalein was found in 15 of 19, including the three negative to the cephalin-cholesterol flocculation test. In most of these cases the function reverted to normal in two to six weeks, but in three it remained abnormal for two to four and a half months. Cohn and Lidman mention one patient who developed chronic hepatitis following infectious mononucleosis.

Evans¹⁴ also studied 19 cases with special reference to the cephalin-cholesterol flocculation test, which gave abnormal results in 90 per cent of the cases but was uniformly negative in a similar group of cases of ordinary infections of the upper respiratory passages. The thymol turbidity was abnormally high in 68 per cent, and the alkaline phosphatase was increased in 43 per cent.

The cases in these studies were all sufficiently severe to call forth the characteristic hematological and serological manifestations of the disease. These observations indicate that hepatitis with readily demonstrable impairment of liver function is a frequent and probably regular manifestation of infectious mononucleosis in its outspoken form. Jaundice occurs in only a small minority of these cases. It is impossible at present to determine how regularly hepatitis occurs in the milder cases which are undoubtedly frequent but often difficult to recognize with certainty with the diagnostic criteria now available.

Recent studies have also shown a close resemblance clinically between many cases of infectious mononucleosis and the milder cases of infectious hepatitis. Severe angina and a marked and rapid enlargement of the regional lymph nodes, when present, are highly characteristic of infectious mononucleosis and rare in infectious hepatitis. Many cases of infectious mononucleosis, however, do not present this picture. Pharyngitis may be mild or absent. Enlargement of the peripheral lymph nodes may be slight, and the predominant symptoms may be malaise, anorexia and gastrointestinal disturbances, with or without fever. As is now well known, many mild cases of infectious hepatitis are not jaundiced, and moderate enlargement of the peripheral lymph nodes is common. Wechsler et al. reported that their jaundiced cases of infectious mononucleosis were clinically indistinguishable from infectious hepatitis except that the jaundice tended to clear more quickly and the digestive disturbances were milder.

¹² CARTER, A. B., and MACLAGAN, N. F.: Some observations on liver function tests in diseases not primarily hepatic, *Brit. Med. Jr.*, 1946, ii, 80-82.

¹³ DEMARSH, Q. B., and ALT, H. L.: Hepatitis without jaundice in infectious mononucleosis, *Arch. Int. Med.*, 1947, lxxx, 257-264.

¹⁴ EVANS, A. S.: Liver involvement in infectious mononucleosis, *Jr. Clin. Invest.*, 1948, xxvii, 106-110.

The specificity of the hematological features of infectious mononucleosis has also been questioned. In infectious hepatitis, particularly in the earlier stages, there is usually a slight leukopenia and relative lymphocytosis together with some atypical lymphocytes resembling those seen in infectious mononucleosis. If not identical, these lymphocytes appear to be at least so similar to those in infectious mononucleosis that they can not be differentiated with certainty by the average observer. Although as a rule they are fewer in number and do not present so striking a picture in infectious hepatitis, Barker et al.¹⁵ have reported that these cells may constitute 60 per cent of the leukocytes. Bizarre lymphocytes, therefore, do not furnish a reliable criterion for the differentiation of the two diseases in an individual patient.

An increase in heterophile agglutinins, however, has not been reported in infectious hepatitis. Although this is not always demonstrable in significant titer in infectious mononucleosis, when present it furnishes the most reliable means of differentiating the two diseases.

These observations are interesting in emphasizing that infectious mononucleosis is a truly generalized infection. Although the mortality is very low, grave complications can develop in exceptional cases. The pathological, clinical and hematological resemblance to infectious hepatitis tempts one to speculate as to a possible biological relationship between the exciting agents of the two diseases. There is at yet, however, no direct or dependable evidence as to the nature of the agent causing infectious mononucleosis.

P. W. C.

¹⁵ BARKER, M. H., CAPPS, R. B., and ALLEN, F. W.: Acute infectious hepatitis in the Mediterranean theater, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 997-1003.

REVIEWS

Penicillin Therapy, Including Streptomycin, Tyrothricin and Other Antibiotic Therapy. By JOHN A. KOLMER, M.S., M.D., Dr. P.H., Sc.D., L.H.D., F. A. C. P., Professor of Medicine in the School of Medicine and the School of Dentistry, Temple University; Director of the Research Institute of Cutaneous Medicine; Formerly Professor of Pathology and Bacteriology, Graduate School of Medicine, University of Pennsylvania. 2nd Ed. 339 pages; 25.5 × 17.5 cm. D. Appleton-Century Company, New York. 1947. Price, \$6.00.

The second edition of this authoritative work keeps it abreast of new advances in the rapidly expanding field of antibiotic therapy. The clinician will find it a dependable reference in selecting the drug and the dosage best adapted for the control of the specific infectious agent to be combated. Methods of administration and of adjuvant therapy designed to prolong the period of absorption or to maintain the blood level by delaying excretion are adequately described. The reasons for failure of antibiotic therapy are discussed. The toxic reactions to the various antibiotics are dealt with in connection with the clinical uses of each drug.

For the clinical pathologist the descriptions of methods employed for the assay of penicillin in various body fluids and for testing the susceptibility of bacteria will be of particular interest.

The major portion of the book is devoted to penicillin but there is also a full coverage of the present status of streptomycin therapy. Tyrothricin and other less important antibiotics some of which have as yet been little employed clinically are briefly discussed.

S. T. R. R., JR.

Diseases of the Chest, with Emphasis on X-Ray Diagnosis. By ELI H. RUBIN, M.D., F.A.C.P., F.C.C.P. 685 pages; 26.5 × 18.5 cm. W. B. Saunders Company, Philadelphia. 1947.

There has been need for a one volume text covering the modern advances in diseases of the chest. Dr. Rubin and his collaborators have produced a book in this field which should meet with wide acceptance both from general internists and from those with a more specialized interest in pulmonary disease. It is written from a clinical point of view by men of wide clinical experience with both the medical and the surgical aspects of diseases of the chest. Moreover it is signalized by the particular attention given to roentgenological diagnosis and by the excellent reproductions of illustrative roentgenograms. The first section of the book contains an adequate discussion of the basic principles of the x-ray and of the technical aspects of its use in diagnosis of chest disease. Other diagnostic procedures, bronchoscopy, bronchography, spirometry, as well as laboratory methods, are not neglected.

The acute bacterial pneumonias, virus pneumonia, the suppurative lung diseases and pulmonary lesions resulting from chemical and physical agencies are dealt with from the aspect of diagnosis and treatment.

There is an important and complete chapter on the rôle of bronchial obstruction in causing pathologic alterations in the physiology of the lung. The many disease conditions that arise from bronchial disease—bronchiectasis, emphysema, pulmonary cysts, etc.—are fully described and the management of these conditions adequately presented.

Note should be made also of the excellent illustrations which add to the value of the chapter on pulmonary neoplasms.

The section on tuberculosis contains a discussion of the epidemiology of the disease. An interesting observation is made concerning the increasing prevalence of primary tuberculosis in the adult. In the diagnosis of pulmonary tuberculosis the predominant rôle of the x-ray is stressed and the often misleading character of physical signs emphasized. Exception might be taken to the statement that active pulmonary disease is excluded by negative sputum and gastric contents. The associations of tuberculosis with pregnancy heart disease and diabetes are viewed more optimistically than in the past. All aspects of treatment of tuberculosis are discussed in some detail.

The section on the principles of surgical treatment of chest diseases is of particular value. The importance of careful preoperative estimation of pulmonary function and of the extent of disease involvement is stressed. The technical surgical problems are discussed. Postoperative treatment is described.

A final and valuable chapter deals with the management of emergencies in chest diseases.

The book will be a valuable acquisition for the libraries of sanatoria and will be helpful to all those who deal with diseases of the chest.

M. W. J.

Renal Diseases. By E. T. BELL, M.D., Professor of Pathology, University of Minnesota, Minneapolis. 434 pages; 23 × 15.5 cm. 1946. Lea & Febiger, Philadelphia. Price, \$7.00.

The author presents in this monograph a comprehensive survey of various conditions of the kidneys with clinical and pathological correlation. There is first a concise presentation of the anatomy and physiology of the kidney. Some concepts underlying the basic pathological physiology are discussed prior to consideration of the clinical and pathological entities. The author uses a wealth of pathological material, which he relates to clinical findings. Each grouping is appropriately subdivided so that comparisons of clinical findings can be made, which may aid the clinician in more accurate interpretation of the pathological lesion. A bibliography is included after each topic, and there is comparison between the author's material and the related publications.

The monograph is a worthwhile contribution to medical literature and is excellent for reference.

E. F. C.

BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Acute Bacterial Diseases: Their Diagnosis and Treatment. By HARRY F. DOWLING, M.D., F.A.C.P., Clinical Professor of Medicine, George Washington University, etc. With the Collaboration of LEWIS K. SWEET, M.D., Chief Medical Officer in Pediatrics and Infectious Diseases, Gallinger Municipal Hospital, etc.; and HAROLD L. HIRSH, M.D., Assistant Professor of Medicine, Georgetown University, etc. 465 pages; 24 × 15.5 cm. 1948. W. B. Saunders Company, Philadelphia. Price, \$6.50.

- Clinical Toxicology*. 2nd Ed. By CLINTON H. THIENES, M.D., Ph.D., Professor of Pharmacology and Head of the Department of Pharmacology and Toxicology, School of Medicine, University of Southern California, etc., and THOMAS J. HALEY, Ph.D., Fellow in the Department of Pharmacology and Toxicology, School of Medicine, University of Southern California. 373 pages; 20.5 × 14 cm. 1948. Lea & Febiger, Philadelphia. Price, \$4.75.
- Conference on Liver Injury*—Transactions of the Fifth Meeting, September 26-27, 1946, New York. Chairman: Dr. C. J. WATSON; Editor: Dr. F. W. HOFFBAUER. 128 pages; 23 × 15.5 cm. (paper bound). 1948. Josiah Macy, Jr. Foundation, New York. Price, \$2.25.
- Diseases of the Skin*. 7th ed. By OLIVER S. ORMSBY, M.D., Rush Professor of Dermatology Emeritus, University of Illinois, etc., and HAMILTON MONTGOMERY, M.D., M.S., Associate Professor of Dermatology and Syphilology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. 1462 pages; 24.5 × 16 cm. 1948. Lea & Febiger, Philadelphia. Price, \$18.00.
- Encyclopedia of Medical Sources*. By EMERSON CROSBY KELLY, M.D., F.A.C.S., Associate Professor of Surgery, Albany Medical College, etc. 476 pages; 23.5 × 16 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$7.50.
- Factors Regulating Blood Pressure*—Transactions of the First Conference, April 24-25, 1947, New York. Edited by B. W. ZWEIFACH and EPHRAIM SHORR. 175 pages; 23 × 16 cm. (paper bound). 1948. Josiah Macy, Jr. Foundation, New York. Price, \$1.90.
- Headache and Other Head Pain*. By HAROLD G. WOLFF, M.D., Professor of Medicine (Neurology) and Associate Professor of Psychiatry, Cornell University Medical College, etc. 642 pages; 24.5 × 16 cm. 1948. Oxford University Press, New York. Price, \$12.00.
- Heart: A Physiologic and Clinical Study of Cardio-vascular Diseases*. By ALDO A. LUISADA, M.D., Instructor in Physiology and Pharmacology, Tufts College Medical School, etc. With a Foreword by HERRMANN L. BLUMGART, Physician-in-Chief, Beth Israel Hospital, etc. 653 pages; 25 × 18 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$10.00.
- Liver Injury*—Transactions of the Sixth Conference, May 1 and 2, 1947, New York. Edited by F. W. HOFFBAUER. 74 pages; 23 × 15.5 cm. (paper bound). 1948. Josiah Macy, Jr. Foundation, New York. Price, \$2.00.
- Psychiatry for the Pediatrician*. By HALE F. SHIRLEY, M.D., Associate Professor of Pediatrics and Psychiatry, Executive Director of the Child Psychiatry Unit, Stanford University School of Medicine. 442 pages; 24 × 16 cm. 1948. The Commonwealth Fund, New York. Price, \$4.50.
- Psychobiology and Psychiatry: A Textbook of Normal and Abnormal Human Behavior*. 2nd Ed. By WENDELL MUNCIE, M.D., Practicing Psychiatrist; Chairman, Medical Advisory Board, Seton Institute, Baltimore, etc. 620 pages; 25 × 17 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, \$9.00.
- Textbook of Gynecology*. 3d Ed. By EMIL NOVAK, M.D., F.A.C.S., Assistant Professor of Gynecology, The Johns Hopkins Medical School, etc. 742 pages; 24 × 16 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$8.00.

COLLEGE NEWS NOTES

NEW YORK, N. Y., SELECTED FOR 1949 ANNUAL SESSION

The Board of Regents of the American College of Physicians, meeting in San Francisco on April 23, chose New York City as the location for the 30th Annual Session. The meeting, which will be held under the presidency of Walter W. Palmer, M.D., F.A.C.P., will take place the week of March 28-April 1, 1949. Further details will be published in subsequent issues of the ANNALS.

ADDITIONAL LIFE MEMBERS

The American College of Physicians is gratified to announce that the following Fellows became life members of the College recently:

Herbert W. Rathe, Waverly, Iowa
H. Russell Fisher, Los Angeles, Calif.
Alan Brown, Toronto, Ont., Can.

A.C.P. POSTGRADUATE COURSES

Spring 1948 Program

The following courses have been concluded with the registration indicated:

No. 1—MEDICAL ASPECTS OF RADIOACTIVITY, U. S. Naval Medical School, Bethesda, Md.; February 18-27; registration, 22, supplemented by approximately 175 medical officers.

No. 2—PHYSICAL MEDICINE FOR THE INTERNIST, Mayo Clinic and Foundation, Rochester, Minn.; March 22-26; registration, 17, supplemented by a number of local physicians.

No. 3—CARDIOVASCULAR DISEASES, University of Southern California School of Medicine, Los Angeles; April 12-17; registration, 47.

The following courses are registered to the capacities indicated and are closed:

No. 4—ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION, Massachusetts General Hospital, Boston; May 10-15; registration, 26.

No. 6—CLINICAL ALLERGY, Roosevelt Hospital, New York City; May 17-28; registration, 8.

The following courses are still open and at time of preparation of this announcement (April 8), accommodations are still available:

No. 5—INTERNAL MEDICINE, Gallinger Municipal Hospital, Washington, D. C.; Wallace M. Yater, M.D., F.A.C.P., Director; May 17-22; present registration, 74; capacity, 100.

No. 7—CLINICAL NEUROLOGY, Jefferson Medical College of Philadelphia; Bernard J. Alpers, M.D., F.A.C.P., Director; May 24-28; present registration, 38; capacity, 75.

No. 8—PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE, University of Illinois College of Medicine, Chicago; A. C. Ivy, M.D., F.A.C.P., Director; May 31-June 5; present registration, 120; capacity, 200.

No. 9—DIABETES AND GENERAL MEDICINE, New England Deaconess Hospital, Boston, Mass.; Elliott P. Joslin, M.D., F.A.C.P., Director; July 12-16; present registration, 35; capacity, 75.

Fees for courses still open—\$30 per week to A.C.P. members; \$60 per week to non-members. Registration forms and detailed outlines may be obtained from the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Tentative Roster of Courses, Autumn, 1948

No. 1—CARDIOLOGY, National Institute of Cardiology, Mexico City; Ignacio Chavez, M.D., F.A.C.P., Director; two weeks, half days devoted to study and half days to inspection and tours; August, 1948; minimal registration, 25—maximal, 75.

No. 2—INTERNAL MEDICINE, University of Pittsburgh School of Medicine, Pittsburgh, Pa.; R. R. Snowden, M.D., F.A.C.P., Director; two weeks, September 20-October 2; maximal registration, 25.

No. 3—RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE, Massachusetts General Hospital, Boston, Mass.; Paul D. White, M.D., F.A.C.P., Director; one week, October or November.

No. 4—ELECTROCARDIOGRAPHY, Emory University School of Medicine, Atlanta, Ga.; R. Bruce Logue, M.D., F.A.C.P., Director; one week.

No. 5—ENDOCRINOLOGY, Chicago Institutions; Willard O. Thompson, M.D., F.A.C.P., Director; one week.

No. 6—GASTRO-ENTEROLOGY, University of Chicago School of Medicine, Chicago, Ill.; Walter L. Palmer, M.D., F.A.C.P., Director; one week.

(Alternate)

No. 6—GASTRO-ENTEROLOGY, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director; one week.

(Alternate)

No. 6—GASTRO-ENTEROLOGY, University of California Medical School and Stanford University School of Medicine, San Francisco, Calif.; Theodore L. Althausen, M.D., F.A.C.P., and Dwight L. Wilbur, M.D., F.A.C.P., Directors; one week.

No. 7—INTERNAL MEDICINE WITH EMPHASIS ON PATHOLOGICAL PHYSIOLOGY—University of Cincinnati College of Medicine, Cincinnati, Ohio; M. A. Blankenhorn, M.D., F.A.C.P., Director; one week, October 11-15; maximal registration, 40.

No. 8—INTERNAL MEDICINE, University of Michigan Medical School, Ann Arbor, Mich.; Cyrus C. Sturgis, M.D., F.A.C.P., Director; one or two weeks.

(Alternate)

No. 8—INTERNAL MEDICINE, University of Minnesota Medical School, Minneapolis, Minn.; Cecil J. Watson, M.D., F.A.C.P., Director; one or two weeks.

No. 9—PSYCHOSOMATIC MEDICINE, University of Colorado Medical Center and the Colorado Psychopathic Hospital, Denver, Colo.; Franklin G. Ebaugh, M.D., F.A.C.P., Director; one week.

No. 10—PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Julius H. Comroe, Jr., M.D., F.A.C.P., Director; one week.

The final selection of the above courses, with possibly one or more additions, will be announced in the next issue of this Journal and a Postgraduate Bulletin will be published in early July. Members are invited to submit suggestions and especially desired courses to the Executive Secretary of the College, and such courses will be arranged if approved by the Advisory Committee on Postgraduate Courses and arrangements for the courses made possible.

MARYLAND REGIONAL MEETING HELD MARCH 27, 1948

An annual Regional Meeting of the members in the State of Maryland, with invitations to members from neighboring territory, including Delaware and the District of Columbia, was held at the Hurd Memorial Hall of the Johns Hopkins Hospital in Baltimore on March 27, with an attendance of 51 Fellows, 34 Associates and 59 guests. Papers were presented by members of the staff of the Johns Hopkins Hospital and Medical School and of the University of Maryland Medical School. A dinner was held in the evening at the Belvedere Hotel with Dr. M. C. Pincoffs as Toastmaster. The meeting was addressed by Mr. John W. Owens, Contributing Editor of the Baltimore Sun, and by Mr. E. R. Loveland, Executive Secretary of the College. The meeting was arranged by Dr. Wetherbee Fort, F.A.C.P., Governor for Maryland.

REGIONAL MEETING, DENVER, COLO., MARCH 2, 1948

The Governors of the College for Colorado, Utah, New Mexico and Idaho jointly arranged a Regional Meeting for members in their states which was held at the University of Colorado Medical School on Tuesday, March 2. The program included medical papers by members and guests during the morning and afternoon. A reception in the evening was followed by a dinner meeting at the Shirley-Savoy Hotel in which the Medical Society of the City and County of Denver and the American College of Surgeons coöperated. The guest of honor and banquet speaker was Walter L. Palmer, M.D., F.A.C.P., Chicago, Chairman of the Board of Governors. The dinner meeting was attended by about 250 physicians.

REGIONAL MEETING, TOPEKA, KANS., MARCH 19, 1948

Some 29 Fellows and Associates of the College and 63 guests participated in a Regional Meeting which was held at the Winter General Hospital in Topeka on March 19. The morning was devoted to a clinical-pathological conference and a business meeting while the afternoon session was devoted to scientific papers by Russell D. Williams, M.D., F.A.C.P., Nathaniel Uhr, M.D., F.A.C.P., Rudolph Chess, M.D. (Associate), Leslie L. Saylor, M.D. (guest), Leslie L. Robbins, M.D. (guest); all of Topeka; and by George F. Corrigan, M.D., F.A.C.P., Wichita, Edward J. Ryan, M.D. (Associate), Emporia, and Frederic W. Hall, M.D. (Associate), Winfield. An informal evening gathering under the auspices of the Topeka Fellows followed. The program was held under the governorship of Harold H. Jones, M.D., F.A.C.P., Winfield.

The Fourth International Congresses on Tropical Medicine and Malaria are to be held in Washington, D. C., May 10-18. The last meeting of the Congresses was held in Amsterdam in 1938. The Congresses will be sponsored by the Government of the United States through its Department of State, and invitations have been sent to more than 60 foreign governments. Other persons and institutions interested in tropical medicine are invited to participate upon the payment of a registration fee. Inquiries regarding the conferences should be addressed to Dr. Wilbur A. Sawyer, Executive Secretary, Fourth International Congresses on Tropical Medicine and Malaria, Department of State, Washington 25, D. C.

The 1948 Annual Meeting of the American College of Chest Physicians will be held on June 17-20 at the Congress Hotel in Chicago, Ill.

Franklin D. Murphy, M.D. (Associate), has been appointed to the Deanship of the University of Kansas School of Medicine, succeeding in that position on July 1, 1948, Harry R. Wahl, M.D. Dr. Murphy is a graduate of the University of Pennsylvania School of Medicine and, for several years, was a member of the Faculty of that school. During the recent war, he was a Captain in the Medical Corps, A.U.S. In addition to becoming Dean, he will be Associate Professor of Internal Medicine.

Rear Admiral George B. Dowling, F.A.C.P., retired from active duty with the Navy on October 1, 1947, and has accepted an appointment as Deputy Administrator of the National Blood Program of the American Red Cross with offices at the American Red Cross Quarters in Washington, D. C.

Samuel Cohen, M.D., F.A.C.P., has recently been appointed Assistant to the Medical Director of the Berthold S. Pollak Hospital for Chest Diseases, Jersey City, N. J.

Colonel Charles C. Gill, (MC), USA, Ret'd, F.A.C.P., of Claremont, Calif., is now a member of the Royal Philatelic Society of London. There is said to be only one other American doctor who is a member of that society.

The American Association for the Study of Goiter held its 1948 meeting at Toronto on May 6-8, under the presidency of James H. Means, M.D., F.A.C.P., Boston, Mass. The program included presentations by many members of the College.

An interesting development in industrial medicine is the program of Conferences on Medical Relations in Business and Industry being held during May and June in Detroit under the auspices of the School of Occupational Health of Wayne University, of which Raymond Hussey, M.D., F.A.C.P., is Dean. The following subjects are covered in these conferences: The Meaning of Human Relations in Industry; Management, Morale, and Productivity; Industrial Human Relations in Action; Basic Fundamentals of Administrative Practices in Operating a Health Service in Industry; Human Problems in Transportation with Special Reference to Aviation; Significance of Non-Occupational Illness in Industry; Significance of Cardio-Vascular Disease in Business and Industrial Employment; Occupational Diseases Today and Yesterday. The conferences aim to present facts which were derived from actual experience in offices and industrial plants, and to stimulate the development of positive preventive measures to insure a high level of manpower in production. The speakers include many distinguished physicians, psychologists and personnel officers.

The sound and color motion picture film, entitled "Management of the Failing Heart," which was first shown at the 1948 Annual Session of the American College

of Physicians in San Francisco, is now available to other medical groups in the country. The text for the film was supplied by the Department of Pharmacology, Cornell University Medical College and stresses the rôle of rest, diuretics, salt-free diet, liquid intake and digitalization in the management of the failing heart. The time consumed in its showing is 40 minutes. It is available to medical societies on request to the producer, Varick Pharmacal Co., Inc., New York, N. Y.

1948 MEMBERSHIP ROSTER QUESTIONNAIRES

Questionnaires designed to elicit information needed in the preparation of the 1948 Membership Roster of the American College of Physicians were mailed out to most Fellows and Masters of the College in March and more recently to other Fellows and to all Associates. The College is forced to limit its publication at this time to a Roster, which will not include biographical data concerning its members, because of present shortage of paper and high printing costs. It is requested that any member who has not yet completed and returned this questionnaire, do so at once, both to assist the College in securing early publication and to insure that the member's listings contain current information.

OBITUARIES

DR. NEIL DUGALD BUIE

On February 9, 1948, Dr. Neil Dugald Buie of Marlin, Tex., died of heart disease after an illness which kept him confined for many months.

Dr. Buie was born in Scotland, Ark., in 1879, but lived almost his entire life in Texas. His premedical education was received at the Sam Houston State Teachers College, from which he graduated in 1902. He attended the University of Texas Medical Department, in Galveston, and the Vanderbilt University School of Medicine, in Nashville, graduating from the latter school in 1907. Dr. Buie later became a Diplomate of the American Board of Internal Medicine.

Dr. Buie settled in Marlin in 1910 and became the owner of the Buie Clinic and Hospital. He was extremely active in medical circles, holding numerous offices in his local, district and state societies, and serving as president of the State Medical Association of Texas, 1941-42. He served as chairman of the Executive Committee of the Federation of State Medical Boards of the United States, and as its president. For fifteen years, he was the health editor of "The Texas Outlook," a monthly publication of the Texas State Teachers' Association. For over twenty years he was a member of the Texas State Board of Medical Examiners. He was a past president of the The Texas Club of Internists. Dr. Buie was a Fellow of the American Medical Association, and a member of the Southern Medical Association, the Military Surgeons Association of the United States, and the Congress on Medical Education and Licensure of the American Medical Association. In 1941 he was made a Fellow of the American College of Physicians.

Dr. Buie's civic activities were wide and varied. He was a member of the Lions Club and a past president of the Rotary Club. He was a deacon of the First Presbyterian Church. He served once in the Electoral College.

M. D. LEVY, M.D., F.A.C.P.,
Governor for Texas

DR. GUSTAVE WILLIAM DISHONG

Gustave William Dishong, M.D., F.A.C.P., was born in San Francisco, November 9, 1874, and died in Omaha, Nebr., November 24, 1947.

Dr. Dishong was graduated from the Creighton University School of Medicine in 1907. He practiced general medicine for three years, which was immediately followed by postgraduate work in neurology and psychiatry in the United States and England. He had been a member of the Faculty of the Creighton University School of Medicine in the Department of Neuropsychiatry since 1912, being appointed Professor and Director of the Department in 1919 and Emeritus Professor in 1939. He was attending neuropsychiatrist at Creighton Memorial St. Joseph's Hospital, and was at one time Consulting Neuropsychiatrist for the Veterans Administration.

Dr. Dishong held the rank of Captain and served in France during World War I with Nebraska Base Hospital No. 49. He was a Diplomate of the American Board of Neuropsychiatry; Fellow of the American Medical Association; Fellow of the American College of Physicians since 1922; member of the Missouri Valley Neuropsychiatric Society, Nebraska State Medical Association and the Omaha-Douglas County Medical Society, serving as President of the latter in 1924.

Dr. Dishong was quiet and reserved. His sympathetic understanding and insight into his patients' problems endeared him to them. He was rated by his students and confreres at Creighton University School of Medicine as an outstanding teacher.

Although Dr. Dishong had been in poor health for several years, he remained¹ in active practice until October 8th.

JOSEPH D. MCCARTHY, M.D., F.A.C.P.,
Governor for Nebraska

DR. JOSEPH SPRAGG EVANS, JR.

Joseph Spragg Evans, Jr., M.D., F.A.C.P., father of the clinical years of medicine at the University of Wisconsin Medical School, and first Professor and Chairman of its Department of Medicine, died on February 3, 1948, at Madison, in the institution which stands as a monument to his effort, the State of Wisconsin General Hospital.

Dr. Evans was born at West Chester, Pa., March 6, 1875, son of a Baptist minister, Reverend Joseph S. Evans, and Ruth Ann (Pierce) Evans. He received his B.A. degree from Haverford in 1895, and then attended the University of Pennsylvania School of Medicine, where he received his M.D. degree in 1899.

His early interests were in the fields of clinical medicine and bacteriology. To prepare himself in these fields he served as an intern from 1899 to 1901, for six months at Germantown Hospital, and for 16 months at The Hospital of the University of Pennsylvania, Philadelphia. Then came a period of study abroad. A few months in Berlin were followed by a year in Vienna in bacteriology with Weichselbaum, and another four months in Paris at the Pasteur Institute as a pupil of Metchnikoff. Returning to Philadelphia in 1902, he engaged in private practice and became an Instructor in Clinical Medicine in the University of Pennsylvania and Assistant Bacteriologist in the William Pepper Laboratory of Clinical Medicine. This first period of his active professional career, essentially one of preparation, came to an end in 1909.

Leaving Philadelphia, Dr. Evans came to the University of Wisconsin in February, 1910 to initiate the development of clinical medicine at the University of Wisconsin. Three years earlier, in 1907, the late Dean Charles R. Bardeen had laid plans for a medical school, and established the first two years of the medical course. The opportunity to carry out these plans and to establish the last two clinical years fell to the new Professor of Clinical Medicine, Joseph S. Evans. He was the first clinician on the campus. He began with the development of a Student Health Service, the second of its kind in the country, of which he was also Director, and in 1915 he set up a student infirmary. From these nuclei grew the entire clinical program. His first teaching was in courses of physical diagnosis and clinical laboratory diagnosis to medical students; he was the outstanding clinician and diagnostician of the community. When Dr. Evans came to Madison, he intended to continue his bacteriological research for which he had been promised adequate opportunity. It soon became obvious that in this new environment his accomplishments were to be in other fields, not less creative than research, but less appreciated in the medical world. Dr. Evans accepted and met the challenge of the new situation with rare versatility. He proved to be a medical statesman with rare talents not only for the Medical School, but also for the entire University. He was not only adviser to successive University presidents and regents, but in 1915 he also became adviser to Governor Philipp. In the following year he became Chairman, Medical Section, Wisconsin Council of Medical Defense. With the opening of the State of Wisconsin General Hospital in 1924 and the establishment of instruction in the clinical years of medicine in 1925, Dr. Evans had won a fourteen years' battle that often had appeared hopeless. At that time his title was changed to Professor and Chairman of the Department of Medicine, and Physician to the State of Wisconsin General Hospital, positions he held until his retirement in 1945.

Lacking the physical strength to carry out his program alone, he showed great ability in developing young men into able clinicians and administrators to whom part of his work was delegated. He provided an atmosphere of harmonious coöperation where others might work freely and unmolested. He fostered a close relationship between the Medical School and the University by the development of the clinical years of medicine on the campus and not at a center of population. Through the development of the preceptorial type of teaching he brought the Medical School into intimate relationship with the profession of the state and extended the campus to the borders of the state. These plans of university education, known as the "Wisconsin Idea," he helped to formulate and sponsor.

In addition to membership in the American Medical Association and its constituent local, state, and county societies, he was a member of Alpha Omega Alpha, Sigma Xi, the Military Order of Loyal Legion, and a Fellow of the College of Physicians of Philadelphia. He was a diplomate of the American Board of Internal Medicine. In 1924 he became a Fellow of the American College of Physicians and an enthusiastic advocate for the College for which he served as Acting Governor in 1945.

In the death of Joseph Spragg Evans, Jr., American medicine, and particularly Wisconsin, has lost another of her great physicians, a public servant whose leadership was dedicated to the task of providing first the facilities and then the teaching of clinical medicine. Along with a personality which was strong and forceful and a courage indomitable and unswerving, he was humble and kind, affectionately known to a wide acquaintanceship as "Joe," to the younger generation as "Uncle Joe," and to his boys as "Chief,"—the heart and soul of the Medical School of the University of Wisconsin.

KARVER L. PUESTOW, M.D., F.A.C.P.,
Governor for Wisconsin

DR. I. WARNER JENKINS

Dr. I. Warner Jenkins of Waco, Tex., died on March 1, 1948, after a lingering illness. Born in Alabama in 1880, he graduated from the Chattanooga Medical College in 1901. After practicing in a small town in Texas for fourteen years, he moved to Waco in 1920 and limited his work almost entirely to radiology.

Dr. Jenkins was a former staff member of the Providence, Johanna McClelland Memorial and Hillcrest Memorial Hospitals, of Waco. He was a Diplomate of The American Board of Radiology, a Fellow of the American Medical Association, and a member of the Texas State Medical Association, the Texas Radiological Society, and the Radiographical Society of North America. Besides his pioneer work in radiology, Dr. Jenkins was an enthusiastic farmer and a breeder of Polled Hereford cattle.

Dr. Jenkins became a Fellow of the American College of Physicians in 1926, the first physician of Waco to be a member of the College.

M. D. LEVY, M.D., F.A.C.P.,
Governor for Texas

DR. REUBEN MACBRAYER

Reuben Adolphus MacBrayer was born in Asheville, N. C., on November 26, 1891. He was the son of Dr. Lewis B. MacBrayer and Lillie Cordelia MacBrayer. He received his A.B. degree from the Wake Forest College in 1911. In 1916 he was graduated from the University of Pennsylvania School of Medicine and almost immediately thereafter entered the Army as a medical officer. He was on active duty in Mexico prior to World War I and later was on active duty in this country.

After World War I, Dr. MacBrayer was on the staff of the North Carolina Sanatorium for a time. He later practiced internal medicine in Shelby, N. C. For a time he was on the staff of the Yale University School of Medicine and the New Haven Hospital, and later was assistant pathologist of the New York Post-Graduate Medical School and Hospital. In 1937 he was appointed Medical Director of Ciba Pharmaceutical Products, Inc., Summit, N. J., and continued in that capacity for the next five years. During this period he was also consultant in endocrinology and associate in pathology for the Overlook Hospital in Summit, N. J.

Dr. MacBrayer volunteered for medical duty in World War II on the day following Pearl Harbor and reported for active duty as a major in the Medical Corps in January, 1942. He continued on active duty throughout the war, serving one and a half years in the E. T. O., first as commanding officer of the 110th Station Hospital and later as hospital inspector, in the office of the chief surgeon, E. T. O. At the time of retirement from the Army, he was a colonel in the Medical Corps, A. U. S. Since his retirement, Dr. MacBrayer had made his home in Southern Pines.

Dr. MacBrayer was a member of the North Carolina State and Moore County Medical Societies, the Association of Military Surgeons, American Society for the Study of Internal Secretions, American Association of Industrial Physicians and Surgeons, National Tuberculosis Association, Southern Medical Association. He was a Fellow of the American College of Physicians, the New York Academy of Medicine, the American Medical Association, and the Royal Society of Medicine of London.

DR. MAX PINNER

Max Pinner died in Berkeley, Calif., on January 7, 1948, at the age of 57 years. His death was due to coronary heart disease. He had been ill, though ambulant and moderately active, for several years. In the final two years, he was well aware of the critical nature of his illness. Although obviously in more than moderate discomfort, he continued completely to fulfill his duties as Editor of the American Review of Tuberculosis, and as consultant in pulmonary diseases to the Veterans Administration, as well as to give regularly of his time and knowledge in the operation of the pulmonary disease services in Alameda County.

Born in Berlin, Germany, he achieved the degree of Doctor of Medicine in 1920 at the University of Tübingen. Shortly thereafter he came to the United States and began his work which led to the acquisition of a notable list of honors and appointments. In 1938, he became Chief of the Division of Pulmonary Diseases, Montefiore Hospital, New York, and held this post until 1946. He was Clinical Professor of Medicine at Columbia University College of Physicians and Surgeons from 1939 to 1946. A Diplomate of the American Board of Pathology, he was best known in this field of endeavor. The American Tuberculosis Association's Trudeau medal for the outstanding contribution in pulmonary tuberculosis went to him in 1947. This distinction afforded him a deep sense of accomplishment.

Like many scholars, he was also a prolific writer, having authored numerous original contributions. His text, "Pulmonary Tuberculosis in the Adult," is a well known reference book. At the time of his death, he was engaged in compiling a book on symptomatology of disease. He felt that physicians who were sufferers of various disease entities, might contribute better descriptions of symptoms. Already, in answer to his published requests, he had received dozens of detailed versions which he considered exceptionally valuable.

Through his death the world has lost one of its scientific men of unusual clarity of thought and originality.

NORMAN LEET, M.D.

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REITER'S DISEASE; REPORT OF FIVE CASES INCLUDING TWO SUCCESSFULLY TREATED WITH HYPERTHERMIA *

By EDWARD W. LOWMAN, Comdr., (Med. Corps), U. S. N., and ROBERT J. BOUCEK, Lieut., (Med. Corps), U. S. N., *U. S. Naval Hospital, Philadelphia, Pennsylvania*

REPORTS of the triad of urethritis, conjunctivitis, and arthritis (so-called Reiter's disease) have appeared more and more frequently in the literature since its initial presentation by Reiter in 1916.¹ This represents in all probability not an increase in the incidence of the condition but a more frequent consideration of the triad in differential diagnosis. On the other hand, however, there have been few reports of successful therapy, and the general tone by inference or conclusion has been that there is no specific treatment for the disease.^{2, 3, 4, 5, 6, 7} In this series, five cases were seen, two of which were treated with hyperthermia and penicillin.

It has been estimated that some 300 cases of Reiter's disease have been reported in the literature.⁸ It is likely that the actual incidence is considerably greater than this figure would indicate. Hollander,⁹ in one report alone, presented 25 cases.

Typical Reiter's disease has its onset with urethritis, which may be mild with a scanty mucoid discharge or more severe with a profuse purulent discharge. The onset is usually sudden. Within several days there develops an acute conjunctivitis, catarrhal or purulent; this may begin unilaterally to be quickly followed by bilateral involvement, or initiate bilaterally. Within days or weeks there then develops an acute arthritis, usually polyarticular. The evolution of the entire triad requires four to eight weeks. It has been reported that the arthritis may be the primary presenting symptom,^{9, 10} or that the conjunctivitis may appear first.^{4, 5} Incomplete syndromes without

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urethritis have been reported.^{5, 8, 9} Diarrhea is often a part of the clinical history; it is rarely bloody or protracted and may constitute so trivial a nuisance as to be recalled by the patient only after very specific interrogation.⁵ Some clinicians consider diarrhea a necessary component of the syndrome, but most feel that it is too inconsistent to be added to the triad as a major diagnostic criterion.^{5, 11}

The disease usually occurs in the younger age groups, especially in the group 20 to 30 years of age. All reports have shown the condition occurring exclusively in males; one reported case in a female was admittedly inconclusive and sufficiently atypical to be dismissed as such.¹²

Etiologically there has been no consistent incrimination of a causative agent. Reiter,¹ in his original observations, believed the condition due to a spirochete (hence the designation "Spirochetosis Arthritica"); this observation has not since been duplicated. Significance has been variously attached to the finding by some investigators of *E. coli*, pneumococci, *Staphylococcus albus*, diphtheroids, "enterococci" of various types, non-hemolytic streptococci, *Bacillus xerosis* and *mucosus*.^{5, 11} Bieglbock¹³ has considered the syndrome allergic in origin. Others have felt that it was a variation of, and indistinguishable etiologically from, the arthritis seen with dysentery^{13, 14}; in substantiation of this, high agglutination titers have been cited.^{5, 13}

Recently, attention has been focused upon the pleuropneumonia-like organisms (so-called "L" organisms) as the possible etiological agent.^{5, 15, 16, 17, 18} These organisms have long been recognized as disease agents in animals, causing contagious pleuropneumonia in cattle, contagious agalactia in sheep, and arthritis or pneumonia in mice and rats. Because of their ability to produce an arthritis in certain animals, they have been used experimentally in the study of the pathology and treatment of this condition in the laboratory. Although most strains are pathogenic, non-pathogenic ones have been isolated from sewage, from decomposing leaves, soil, and manure, and from lesions of foot-rot in sheep.

"L" organisms are pleomorphic in nature, varying in form from minute elementary bodies and spherules to asterodiscules and branching filaments. They are filtrable through gradacol membranes down to about 0.4 μ in pore diameter. They do not, on smear, stain with the usual bacteriologic chemicals but require prolonged staining with Giemsa stain. Furthermore, they do not culture on ordinary media but require rich media containing 10 to 40 per cent serum. These features are of importance in the evaluation of certain negative reports of investigations in humans.

A search by Sabin¹⁷ for pleuropneumonia-like organisms in the throats of humans was unsuccessful. Dienes and Smith¹⁶ in a large series of cervical smear cultures found these organisms to be a frequent inhabitant of the female cervix and vagina and concluded that though they might, like many other organisms, be of a nonpathogenic nature, it was probable that either

alone or in combinations with other organisms they could produce a clinical picture similar to gonococcal infection. In four cases of chronic prostatitis in males the organisms were cultured (in three from prostatic fluid; one from the urethra); no gonococci were found. Of these four patients, one had rheumatoid arthritis, one had a polyarthritis resembling gonorrheal arthritis, and a third had soreness of the feet and knees and swelling of the fingers. Among nine non-gonorrheal females from whom the "L" organisms were isolated, one had rheumatoid arthritis, and three complained of various skeletal aches and pains. Thus, it was thought by these investigators that this occurrence of arthritis symptoms in humans might be of particular interest in view of the arthritis syndrome occurring both naturally and experimentally in animals as a result of infection with these organisms.

Wallerstein et al.¹⁵ conducted agglutination evaluations on a series of 102 patients having rheumatoid arthritis, ulcerative colitis, various chronic arthritides, and diarrheal conditions. Suggestively high titers were obtained only in the small group of probable Reiter's disease and in two of five cases of various combinations of conjunctivitis, urethritis, and cervicitis; in this latter group four of the five patients were females. Of the Reiter's group, two cases definitely satisfied the clinical criteria for diagnosis. Of these two cases, pleuropneumonia-like organisms were cultured from the urethra of one; the agglutination titer in this case during the acute phase of the illness was high (1:64), and 18 months later during remission of the disease was negative. In the second case, during the acute phase of the illness the agglutination titer was high (1:32), and three months later when completely well it was negative. In a third patient whose diagnosis as Reiter's disease was probable but less certain, the agglutination titer was never significant.

In cultures of washings from the urethrae of 24 cases of non-specific urethritis, Beveridge¹⁷ found "L" organisms in four instances. He felt that although no conclusions could be reached, the best possibility was that the organism normally was a saprophytic inhabitant of the female genital tract and that after transfer through sexual contact it might, in the male, under certain conditions of virulence and dosage set up a pathologic condition.

The matter of etiology is, therefore, far from settled. So also is the question of the rôle of sexual contact; proponents^{5, 16, 17} and opponents^{2, 6, 9, 11, 19} have presented statistical evidence in case histories regarding the rôle of sexual exposure in the precipitation of the disease. One author⁵ has proposed that the "L" organism is the precipitating agent and that in diarrheal cases the entrance is via the gastrointestinal tract whereas in non-diarrheal cases it is via the genital tract.

Harkness¹⁸ supports the "L" organism hypothesis and states that he has found inclusion bodies in the urethral and conjunctival smears from every one of five cases of Reiter's disease seen by him in a five-year period.

Rosenblum² cites the case of a male patient who developed the typical

Reiter triad twice (with a two and a half year interim) following intercourse with the same female.

In laboratory studies of synovial fluid, including the search for "L" organisms, significant etiological findings have never been noted.^{11, 13, 16, 20}

In reporting microscopic studies on one case in which an arthrotomy was performed, Hollander noted that the limitation of the intense hyperemia to the superficial layers of the synovium was in marked contrast to the findings seen in true rheumatoid arthritis.

The course of Reiter's disease is usually two to five months, culminating in complete remission. Unless complicated, the urethritis and conjunctivitis are transient within days or weeks, but may recur at any time during the course of the disease. The arthritis is the major disabling feature and persists for months. Any joints may be affected, although the weight-bearing joints especially are prone to involvement; the distribution may simulate that of rheumatoid arthritis or there may be monoarticular involvement. The process is acute, with pain, tenderness, swelling, increased heat, and commonly hydroarthrosis. Roentgenologically, osteoporosis is the most common finding in involved joints. Periosteal proliferation is noted less frequently; actual bone destruction is rare but may occur.^{9, 12, 19}

Generalized lymphadenopathy^{5, 8, 10} and occasionally splenomegaly^{12, 21} have been reported. Rarely is the course septicemic. A mild elevation of temperature is common during the acute arthritic phase. Contrary to specific infectious arthritis, the onset of the joint manifestations is without an initial chill. The sedimentation rate is moderately elevated and the white blood count shows a moderate increase in polymorphonuclear cells. Both the elevation in sedimentation rate and that of the white blood count parallel the acuteness of the disease episodes. A secondary hypochromic anemia may develop.^{7, 11} Urinalyses show clumps of pus cells, occasional red blood cells, traces of albumin, and rarely casts. Bacteriologic, immunologic, and microscopic studies of exudates, tissues, cavity fluids, and blood have their greatest value in a negative way in the exclusion of gonorrheal arthritis.

The common urologic manifestation of the disease is usually a transient urethral discharge, scanty or profuse, mucoid or purulent, with or without associated dysuria and hematuria; there is often a concurrent catarrhal prostatitis. However, prostatic abscess, vesiculitis, hemorrhagic cystitis, hydronephrosis, pyelonephrosis, and ureteral obstruction may complicate the normal course of the condition and pose major urologic problems.^{2, 7, 10, 22} Ulcerations about the meatus or glans penis are not uncommon and may give rise to balanoposthitis.

The conjunctivitis is acute, purulent, and usually bilateral, with tendency to spontaneous remission without corneal ulceration; iritis and keratitis have been infrequent complications. Resolution is without residua.

Cutaneous lesions may present themselves as simple erythemas, urticarial or erythema nodosum-like lesions, hyperkeratotic lesions, or as hemor-

rhagic or vesicular eruptions. Erythema of the buccal mucous membrane with vesicle formation and ultimate denudation, pharyngeal congestion, superficial glossitis, and vesicular eruptions of the lips have been reported.⁷ Harkness¹⁸ has reported 20 cases of keratoderma blennorrhagica, of which seven were associated with a non-specific urethritis (the remaining 13 being concurrent with gonorrheal urethritis). In our cases the only skin manifestation seen was in the one case (Case 1, R. P.) with vesicular penile lesions.

The disease, generally speaking, is self-limited, terminating within months without residua or sequelae. In only a few instances^{5, 19} have persisting deformities or disabilities as a result of the arthritis been reported. The predisposition to relapse, however, is high. Probably as many as 25 per cent of cases suffer recurrences^{10, 11, 20}; these occur after varying intervals, a period of 16 years having been reported in one case.⁵

The treatment of Reiter's disease has been palliative and non-specific and, on the whole, has been ineffectual in shortening the course of the condition. The sulfa drugs, penicillin, myocrisine, arsenicals, salicylates, and numerous other drugs have provided little relief.^{2, 3, 4, 5, 6, 7, 19} Having learned of the subsidence of symptoms in a patient who had experienced a febrile reaction to sulfadiazine, Strachstein²³ in 1945 treated a Reiter's case with artificial fever using protein shock therapy. This patient had had his disease for one year. After two sessions of fever and within two weeks, the patient was asymptomatic and discharged from the hospital; an eight months' follow-up showed no recurrence of symptoms. Vallee,⁵ on the other hand, after treating one case with artificially induced fever reported negative results. Beiglbock¹³ and Harkness¹⁸ both have reported favorable results with protein-shock type of fever therapy. Sargent⁷ expressed the feeling that repeated foreign protein shock in the form of typhoid vaccine intravenously definitely benefited eye and joint manifestations.

Five cases of Reiter's disease are included in this series. All but one presented the complete triad; the fifth did not present the typical eye symptoms but probably represented an incomplete form of the disease.

CASE REPORTS

Case 1. R. P., a 24 year old white male, was admitted to the sick list on December 17, 1945 complaining of swelling, stiffness, and pain in both knees.

From January 1944 until October 20, 1945 this man was overseas and during this time had no venereal exposures. Upon his return to the United States in October 1945, he began drinking heavily and having frequent intercourse (five times a week). On the three successive nights prior to his present illness he had had intercourse and had been drinking to excess. On November 25 there developed a scanty, mucoid urethral discharge which amounted to only a few drops a day. There was no associated hematuria or dysuria. One urethral smear was negative for gonococci. The discharge subsided spontaneously after four days. One week later the right eye became sticky and reddened, followed in four days by involvement of the left. A diagnosis of acute conjunctivitis was made and treatment consisted of sulfadiazine eye

drops and sulfadiazine orally, 15 grains three times a day; there was no apparent response to this therapy, the eye symptoms persisting for six weeks. Three days after the onset of the conjunctivitis, the patient developed an "achy feeling" in both popliteal spaces as if he had "been exercising too much." Swelling and pain developed progressively over the next 10 days so that the patient was unable to climb stairs and on level ground had to "shuffle along."

Upon admission, both knees were warm and swollen. Urinalysis showed a trace of albumin, occasional fine granular casts, and two to 12 white blood cells per high power field. The white blood count and hemoglobin determinations were normal. The blood sedimentation rate was 28 mm. in one hour; the blood Kahn reaction was negative. Roentgenograms of both knees showed no abnormal findings. On December 22, 1945 penicillin intramuscularly was started, 20,000 units four times a day, and a total of 600,000 units was administered with no apparent benefit. A culture of the fluid from the right knee was negative; that from the left knee showed a growth of hemolytic *Staphylococcus aureus* which was considered a contaminant. Because of flexion contractures appearing in both knees, bilateral Buck's extension traction was applied on January 7, 1945. During his first six weeks of hospitalization, the patient ran a low-grade afternoon fever spiking to 99 to 100.4° F. After three weeks of traction, the swelling and contractures of the knees improved and the patient was permitted up for bathroom privileges. Over the ensuing month he was graduated to an up-patient status. On January 31 the patient had a mild transient episode of diarrhea which responded promptly to symptomatic treatment. By February 28 the sedimentation rate had fallen to normal (10 mm. in one hour).

Late in March 1946, some seven weeks after coming out of traction, the patient overnight developed acute tenderness in the right ankle and in both knees with associated swelling and pain. Two days later there again developed bilateral conjunctivitis, and the mucoid urethral discharge reappeared. At the same time the patient developed acute diarrhea with 10 watery stools over a 24 hour period; the latter responded to symptomatic treatment. Despite treatment with sulfadiazine, penicillin, and local measures for the conjunctivitis, the urethritis and eye symptoms persisted for a month. Urethral smears were negative. Several small dusky red vesicles without induration or ulceration appeared on the glans penis; repeated darkfield examinations and blood Kahn reactions were negative. During this time the blood sedimentation rate again began to rise, reaching 22 mm. in one hour by May 9, 1946. In May a bivalved cast was placed on the right leg below the knee for one month to immobilize the ankle. In June there was a transient recurrence of the urethral discharge.

In July 1946, the patient was given five sessions of hyperthermia with fever sustained at 105° F. for five hours each. These were given twice a week. For 24 hours preceding and 24 hours following each fever session, he was given 20,000 units of penicillin every two hours. During the hyperthermia, 100,000 units of penicillin intravenously in 5 per cent glucose in saline was administered as the fever leveled at 105° F.

Prior to initiation of the fever there were moderate tenderness and swelling and marked stiffness of the right ankle, moderate tenderness and swelling of the right knee, and slight swelling and tenderness of the left knee. Following the first session of fever, the patient was able to walk without limping. There was progressive improvement both objectively and subjectively after each session of fever so that by the end of the fifth, he was sufficiently improved to be allowed to go on 30 days' leave.

Shortly after return from leave, the patient developed a slight mucoid urethral discharge, low-grade eye inflammation, and mild aching in the ankles, knees, and low back. This required no treatment and did not necessitate return to bed. After three weeks, there was no residua, and the patient was discharged.

A follow-up examination on January 6, 1947 revealed only minimal tenderness at the arch of the right foot. Subjectively the patient had been well since discharge and had regained all weight lost during his hospitalization.

Case 2. C. S., a 22 year old white male, was admitted to this hospital on July 25, 1946, complaining of persistent pain and swelling in both ankles.

On January 15, 1946, 10 days following sexual exposure, this man developed a purulent, moderately severe urethritis with associated dysuria. Five urethral smears were negative for gonococci. He was treated with sulfa drugs for four days; the discharge subsided after 10 days. Eleven days following the onset of the urethritis the patient developed an acute bilateral catarrhal conjunctivitis; this subsided in five days under local therapy.

On February 5, 1946, three weeks following the onset of the urethritis, the right ankle became markedly swollen, red and tender. This persisted and spread within the next three weeks to involve the third and fifth right toes and the left ankle so that he was unable to walk and lost considerable sleep. He was then admitted to a Service hospital and was treated with local diathermy and massage without benefit. At no time did the patient have diarrhea or skin lesions.

On admission to this hospital on July 25, 1946, the patient was still unable to walk. There was moderate tenderness about both arches and internal malleoli, marked tenderness about the os calci, and slight tenderness at the right second, third, fourth, and fifth metatarsophalangeal joints. Roentgenographic examinations of the feet and ankles showed no evidence of bony pathology. The blood sedimentation rate was normal. A trial of whirlpool baths, local diathermy, and massage for eight days aggravated the joint symptoms. The patient was then started on penicillin and hyperthermia. He received five sessions of fever of 104 to 106° F. of five hours' duration each given twice weekly. For 24 hours prior to each session and 24 hours following each session the patient received 20,000 units of penicillin intramuscularly every two hours (total 480,000 units). Following the induction period in the hyperthermia and during the height of the fever, he received an additional 100,000 units of penicillin intravenously with 1000 c.c. of 5 per cent glucose in saline.

Following the first fever session the patient was markedly improved and for the first time since the onset of his illness he was able to walk comfortably. With each succeeding treatment there was progressive improvement.

On September 15, 1946, upon the completion of his five fever sessions, the patient was discharged asymptomatic.

On March 29, 1947 the patient was seen for recheck. There had been no recurrence of symptoms, and examination was negative.

Case 3. L. L., a 23 year old white male, was admitted to the hospital on April 5, 1946. In August 1945, one week following sexual exposure, this patient developed a scanty mucopurulent urethral discharge without dysuria or hematuria. He was seen by a civilian physician. Smears were negative for gonococci, and treatment with penicillin (amount unknown) was started. Several days later there developed an acute conjunctivitis of the right eye which was treated and responded to local therapy. Two weeks after the initial onset of the urethritis, there developed acute low back pain, then pain and swelling of the metatarsophalangeal joints of the right foot, pain about the left hip joint, swelling and tenderness of the right second metacarpophalangeal joint and of the right knee. He was admitted to a civilian hospital and treated for five months with urethral irrigations, prostatic massages, two courses of penicillin (amount unknown), argyrol injection of seminal vesicles by vasopuncture, diathermy, and three bouts of intravenous typhoid fever vaccine. During this period there was progressive improvement. By April 1946 progress had become static and the patient was referred to the Naval Hospital with the recommendation that he be given hyperthermia. Upon admission on April 5, 1946, the patient presented slight swelling and

tenderness of the right knee, moderate tenderness about the second, third, and fourth metatarsophalangeal joints of the right foot, moderate tenderness about the left heel, slight tenderness at the right second metacarpophalangeal joint, and moderate bilateral sacroiliac tenderness to percussion. There was no redness nor increase in joint warmth. The blood sedimentation rate, urinalysis, and routine blood counts were all normal. Roentgenological examinations revealed slight osteoporosis of the bones of the left hip, right knee, and both feet; there was a small hypertrophic spur on the anterior border of the right patella. Prostatic examination was normal. During his hospital stay the patient had an occasional morning "tear" from the urethra; smear examination of this discharge showed numerous white blood cells but no organisms. On the basis of the history and the findings a diagnosis of Reiter's disease (nearing remission) was established, and conservative physiotherapeutic measures were instituted. In the course of two months there was gradual improvement. By June 17, 1946 the patient was ambulatory and was discharged.

Case 4. C. J. L., a 24 year old white male, was first admitted to the hospital in July of 1946.

In June of 1946, 10 days following sexual exposure, this patient developed a scant mucoid urethral discharge with increased urinary frequency but with no hematuria or dysuria. He was seen by his family physician who felt that he had a non-specific urethritis and treated him with prostatic massages with little benefit. A urethral smear at this time was negative. One week following the discharge there developed acute redness, swelling, and tenderness in the right great toe and over the dorsum of the right foot.

Upon admission to the hospital on July 26, 1946, examination revealed marked swelling and tenderness about the right great toe; there were redness and increased heat extending onto the dorsum of the foot. The temperature was 101° F. The white blood count was moderately elevated; urine showed a trace of albumin and under high power field was loaded with leukocytes. A blood Kahn reaction was negative; a sedimentation rate was not obtained. Because of a concurrent epidermophytosis, a diagnosis of acute cellulitis was made and the patient was treated with penicillin, 30,000 units every three hours. In the course of nine days there was considerable improvement. During his hospital stay there developed an acute conjunctivitis of the left eye and then of the right which responded after a week of treatment with boric acid irrigations and local sulfathiazole ointment. The patient was discharged after nine days' hospitalization.

Several days following release from the hospital the patient developed acute aching in the right knee which rapidly became worse, with swelling, stiffness, and pain, and which spread similarly to involve the left. He again consulted his family physician who advised physical therapy and the use of liniments. During the next four weeks there was no improvement and on September 16 the patient was readmitted to this hospital.

Upon readmission, examination showed both knees to be swollen and warm, the left being more edematous than the right. There was no marked subjective pain, but the patient complained of "stiffness." There was slight tenderness laterally about the right knee and medially about the left and marked atrophy bilaterally of the quadriceps muscle groups. The first metatarsophalangeal joint on the right was enlarged and slightly tender. Temperature on admission was 99.6° F. Urinalysis and blood studies were normal except for the sedimentation rate which was found to be 22 mm. in one hour. An electrocardiogram was normal. Roentgenological studies showed moderate demineralization of both knees and of the right foot with some narrowing of the joint spaces.

A conservative régime of rest, local heat and massage, and active quadriceps exercises was instituted and the patient improved progressively. He was graduated

to reambulation training and active resistive quadriceps exercises in the remedial exercise gymnasium. By December 30, 1946 the blood sedimentation rate was normal, the patient's symptoms had subsided without residua, walking tolerance was good, and he was accordingly discharged from the hospital three and a half months following his readmission.

Case 5. L. H., a 26 year old male, was first seen on January 10, 1947, complaining of pain and swelling in both feet.

In September of 1946 he had awakened one morning with the left foot acutely swollen, tender, and warmer than the right. The patient attributed this to pes planus and the fact that on the previous day he had climbed stairs carrying three sea bags. The tenderness at this time was in the arch, at the proximal end of the fifth metatarsal, and at the metatarsal heads. Two days later the right foot became similarly involved overnight; again the patient attributed the symptoms to pes planus and a sprain of the ankle. Several days following the onset of the foot symptoms, there developed a severe diarrhea with stools every one to one and one-half hours, with associated tenesmus but no blood. The foot symptoms persisted. The diarrhea lasted only a couple of days; the patient attributed the cessation of this to the fact that he stopped drinking. Two weeks following the foot symptoms there developed a mucoid urethritis with associated dysuria but no hematuria. For this he was treated with penicillin (200,000 units) although a smear of the urethral discharge was negative for gonococci. The urethritis did not respond promptly to the penicillin but subsided some four days after the penicillin was discontinued. There were no ocular symptoms during this illness. The foot symptoms persisted so that walking was difficult. Treatment consisted of an ineffectual trial of luminous heat, massage, and salicylates, the latter providing some palliative relief. The patient was told that his sedimentation rate was too high to grant a request for return to duty status. In the period between September 1946, and his admission to this hospital, there was gradual improvement in the status of the feet. There was no recurrence of the diarrhea or the urethritis. There occurred some subjective stinging of the eyelids but nothing abnormal was noted objectively.

The patient gave no history of previous joint symptoms. In February 1946, for two weeks, he had had pain in the adductor muscles of the right shoulder which cleared spontaneously. During the present illness the knees and fingers periodically had been achy. There had been episodes of slight swelling about the knees, but these were never severe or persistent.

At the time of onset of illness the patient was on Rear Echelon duty in China. He had had no upper respiratory infections. His work entailed pumping water from cellars, operating showers, and otherwise staying wet most of the day. Most meals were eaten at the regular mess, though he had eaten elsewhere among civilian Chinese at times. There were no other instances of diarrhea among other Marines whose habits were similar.

During his stay in China prior to illness (November of 1945 to September of 1946) he had consumed considerable alcohol, averaging eight to 10 bottles of beer a day and two quarts of vodka a week and had had sexual exposure almost nightly for 11 months prior to his illness but always with the same person. The only weight loss was 15 pounds at the onset of his present illness which loss the patient attributed to poor hospital food. This weight loss at the time of our report had been completely regained.

On admission to this hospital the patient showed swelling of the right foot plus periarticular thickening about the lateral and medial malleoli. There was 1° tenderness at the arch, about the malleoli, at the os calcis, and the calcaneal bursa. There was no deformity, and the range of this ankle was normal. On the left there was slight swelling about the malleoli with no tenderness. There was swelling at the

proximal end of the fifth metatarsal with 2° tenderness and 2° tenderness at the arch. There was no deformity, and the range of this ankle was normal. The impression on admission was that this was a case of Reiter's disease without the conjunctival symptoms.

Because it was felt that this patient's disease was considerably improved and nearing spontaneous remission, the fever and penicillin régime was not recommended. He was treated symptomatically with physiotherapeutic measures. At the time of this report, after four months, he had improved but still presented a 25 per cent residua which precluded his immediate return to duty. There had been no recurrence of either the urethral or the gastrointestinal symptoms.

DISCUSSION

The five cases of Reiter's disease presented here were all chronically ill patients. There had been no significant response to various forms of therapy.

In the case of R. P., there was immediate improvement following the first fever-penicillin session. He had been ill for eight months. After one month of treatment he had become progressively asymptomatic and was discharged from the hospital on 30 days' convalescent leave. A four months' follow-up examination showed minimal residua.

The second case, C. S., treated with fever and penicillin had been unable to walk for six months because of his joint symptoms. After the first fever session he walked, and after five sessions was completely asymptomatic. Within two months of his initial fever treatment he was back at work. A six months' follow-up examination showed no subjective or objective residua.

The rationale for the use of hyperthermia combined with penicillin in the treatment of Reiter's disease has not a very sound basis. The success of protein shock fevers in some cases reported in this country and abroad by a few writers^{7, 13, 18, 23} was the initial stimulus. Because of the fact that most organisms have been shown to be thermostable to temperatures tolerated by the human body,²⁴ it was felt that the addition of penicillin might effect a synergistic action with the fever much as that seen with the use of combined fever and penicillin in neurosyphilis, and with fever and sulfa drugs in resistant gonorrhea or gonorrheal arthritis.

It is still to be seen whether fever alone or if variants of the fever régime employed here might not prove effective per se. The use of penicillin alone has been shown through failures in these and other reported cases to be ineffective therapy. Further observations in treating larger series of cases should better standardize optimum treatment régimes.

The important implication is that the two cases treated with combined fever and penicillin apparently responded specifically, and if this can be further substantiated it will mean a substantial reduction in the morbidity of a protracted disease process.

The case of L. H., who, upon admission, was thought to be approaching quiescence and who, therefore, was handled conservatively without fever, probably should have been submitted to the fever-penicillin régime. After four months of conservative management he still retained 25 per cent residua.

SUMMARY

1. Five cases of Reiter's disease have been presented. Four are typical cases with the classical triad of symptoms while the fifth probably represents an incomplete syndrome without the conjunctivitis.

2. Two of the cases presenting the complete triad responded to treatment with artificial hyperthermia and penicillin and promptly went into remission. These cases had been chronically ill for six and seven months respectively. Follow-up examinations after four and six months respectively showed no recurrence.

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HISTOPLASMIN AND TUBERCULIN SENSITIVITY IN RELATION TO PULMONARY CALCIFICATIONS AMONG UNIVERSITY OF WISCONSIN STUDENTS*

By HELEN A. DICKIE, M.D., and ELIZABETH A. CLARK, M. D.,
Madison, Wisconsin

IN the last few years the problem of the marked variation in the frequency of pulmonary calcifications as observed in chest roentgenograms has been studied by several groups.^{2, 3, 4, 5, 6, 7, 9} The highest incidence of pulmonary calcifications has been found in the central eastern half of the United States. These areas were not closely correlated with the areas of highest mortality from tuberculosis. Because a number of reports had demonstrated that a large number of these individuals had negative tuberculin reactions, a search for a non-tuberculous etiology was started. Smith¹ pointed out that the area of high incidence of pulmonary calcifications corresponded with the incidence of histoplasmosis. Palmer² studied the histoplasmin and tuberculin reactions in approximately 3000 student nurses and found that the incidence of histoplasmin reactions was high in the same areas where the reported that four times as many student nurses and found that the monary calcifications as in Philadelphia, and that over four times as many of them were positive to histoplasmin. However, the tuberculin sensitivity was approximately the same in these two student groups. Furculow, High and Allan⁶ reported from a study of over 17,000 persons in Kansas City that the frequency of pulmonary calcifications was over twice as high in the reactors to histoplasmin alone as to tuberculin alone.

Zwerling and Palmer⁵ concluded that it was impossible to distinguish roentgenographically between the calcifications that occurred in the tuberculin positive and histoplasmin positive individuals. In a later study High et al.⁸ reported that disseminated pulmonary calcification in 108 individuals was associated with a positive histoplasmin test in 104 instances and none of these individuals reacted only to tuberculin.

Our interest in the problem of pulmonary calcifications in the tuberculin negative individual was increased by the reports of Palmer and others^{2, 3, 4} on the close correlation of histoplasmin sensitivity with pulmonary calcifications. The routine tuberculin testing and photofluorography of the students entering the University of Wisconsin allowed the isolation of a group of stu-

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From the Departments of Student Health and Radiology, University of Wisconsin, Madison, Wisconsin.

The histoplasmin used in this study was supplied by M. L. Furculow, M.D. of the United States Public Health Service.

dents who were tuberculin negative, but whose photofluorograms were interpreted as showing evidence of pulmonary calcifications or infiltrations. In the fall of 1945 each student was tested by the usual intradermal technic using the first and second strength P.P.D. The tests were read at 48 hours and a reaction of 5.0 mm. or greater of edema and redness was recorded as a positive reaction. From approximately 5000 students examined in this manner, a group of 160 was found to be tuberculin negative and to have pulmonary calcification or, much less frequently, infiltration roentgenologically. In April 1946, 116 of these students completed the retesting program which consisted of a tuberculin test using 1.0 mg. O.T. and 0.1 c.c. of a 1:1000 dilution of a histoplasmin solution. Both tests were given intradermally and read at 48 hours. A reaction of 5 by 10 mm. induration was required before the test was regarded as positive. The reactions to histoplasmin were clear cut and varied from 10 to 40 mm. in diameter. Of the 116 who completed the test, 67 were histoplasmin positive. None of the tuberculin tests was positive although the intervals between tuberculin tests varied from two to six months.

From these results it was apparent that we were dealing with an unusually high percentage of pulmonary calcifications unassociated with positive tuberculin or histoplasmin reactions. Palmer² reported 1.2 per cent calcification in 2141 student nurses who were negative to both antigens. Obviously, the first step was to check the accuracy of the roentgen interpretation of pulmonary calcifications. These 4 by 5 stereo photofluorograms had been interpreted routinely by one of us (E. C.). In routine reading of photofluorograms we believe the tendency to interpret vascular markings as calcification is greater than in the conventional 14 by 17 chest roentgenogram. Therefore, the photofluorograms of the 116 individuals were reviewed by the two of us independently. The few on which we differed were reexamined and we agreed on the presence or absence of calcification. From this review of 116 photofluorograms we concluded that the diagnosis of calcification was not justified in 32. In 79 we agreed that calcification probably existed and that in five others there was pulmonary infiltration without calcification. These interpretations were made without the knowledge of the histoplasmin sensitivity.

In correlating these results with the histoplasmin reaction we found that 61 of the group who had the roentgen diagnosis of calcification were histoplasmin positive as were the five with non-calcified pulmonary infiltrates. The majority of these students showed extremely large calcified areas both in the hilum and in the parenchyma. Some of these areas were only partially calcified. In the 49 students who failed to react either to tuberculin or histoplasmin, there were 18 in whom we agreed calcification probably existed although the size, irregularity and density of the roentgen shadows were not such that we were certain of the diagnosis. To arrive at a more accurate classification of this group, we examined them fluoroscopically. Fourteen

of the 18 were available for study, as four were no longer in school. By fluoroscopy calcification was found in three; one with a relatively large left hilum calcification and two with peripheral calcifications 2.0 to 3.0 mm. in diameter. In the remaining 11 we concluded that no calcification existed although the large and prominent vascular markings thought to be probable calcified areas on the photofluorogram were usually discernible.

If we include the four not available for fluoroscopy in the group as showing calcification (and that seems improbable) we have a total of seven of 73 with calcification, or 9.6 per cent who failed to react either to tuberculin or to histoplasmin. This correlates very closely with Palmer's² study in which he found 25 of 294 or 8.5 per cent who had the roentgen diagnosis of calcification but were negative to histoplasmin and tuberculin. In our study coccidioidin skin testing was not done routinely as these students had no exposure in the areas where *Coccidioides immitis* is endemic. On 10 of the group who were retested at a later date with coccidioidin no positive reactions were noted.

All the students with positive histoplasmin tests were questioned as to their residence exclusive of their army experience. If a student had lived five-sixths of his life in one state, that state was tabulated as his residence. Wisconsin and Illinois led the represented states with 14 students each. Ohio was next with seven. Kentucky, Tennessee, New York, Mississippi, Maryland and Indiana were each assigned three students; Iowa, Oklahoma and the District of Columbia, two students each. One student was assigned to each of the states of Texas, Arkansas, Connecticut, Delaware, Nebraska. Comparison of the distribution of histoplasmin reactors according to residence with the number of students enrolled in the university from each of these states revealed an obvious disproportion in the incidence of histoplasmin sensitivity, the incidence among Wisconsin students being lower by actual percentage.

The second part of the study was done to determine the incidence of histoplasmin sensitivity in Wisconsin students. All the students entering in June 1946 were tuberculin tested as previously described and were also given 0.1 c.c. of 1:1000 histoplasmin solution intradermally. The readings were made as noted before. In this and in the succeeding group, 70 mm. photofluorograms were used instead of 4 by 5 stereo photofluorograms. Not considering army experience, we classified 381 students as lifetime residents of Wisconsin. Of these, 350 were men and 31 women. Forty-four positive histoplasmin tests were recorded, or 11.5 per cent. Tuberculin sensitivity was noted in 125 or 33 per cent. In 12 students both the histoplasmin and tuberculin test were positive. At this same time 184 students who were residents of the United States, but not Wisconsin residents, were tested. The number of foreign students tested was 12 which is too small to be significant. Only one of these 12 had a positive histoplasmin test and she had

spent her entire life in western Canada. Of the 184, 50 or 27.6 per cent were positive to histoplasmin. The tuberculin sensitivity was 41.3 per cent.

The states represented in the histoplasmin positive group were essentially the same as noted in the previous group with pulmonary calcifications; i.e., the central eastern states. The number was not large enough to be statistically significant if determined in percentages of the total students tested from the various states. Since it has been reported by Palmer⁴ that states vary in histoplasmin sensitivity in different areas, we attempted to determine the situation among the reactors from Wisconsin. From this standpoint we divided the state into northern and southern parts. As Milwaukee is the only large city and is on the lake shore, we listed it separately. From northern Wisconsin there were eight histoplasmin reactors in 61 or 13.7 per cent. From Milwaukee eight of 66 were sensitive to histoplasmin or 11.6 per cent. In the rest of southern Wisconsin there were 28 positives from 252 individuals or 11.1 per cent. Therefore, we concluded that there was no significant variation in histoplasmin sensitivity in the various regions of Wisconsin, nor in the urban and rural populations.

Because the number of women in the previous group was small we tested the women who entered school in the fall of 1946 by the same method. One thousand eighteen students completed their skin testing. Eight hundred ninety-four of these were lifetime Wisconsin residents. Only 24 or 2.6 per cent were histoplasmin positive. Among the women from states other than Wisconsin 19 histoplasmin positive individuals were found in 124 or 15.3 per cent. Tuberculin sensitivity was found in 155 or 17.2 per cent of the Wisconsin women. In the non-resident group 27 of 124 or 21.7 per cent were positive to tuberculin. Again the out-of-state students who reacted to histoplasmin were scattered through the same group of states where histoplasmin sensitivity has been shown to be high.

In addition to studying the incidence of histoplasmin sensitivity in these students, we were interested in the incidence of calcification in the various groups as classified according to skin tests. For purposes of more accurate diagnosis of calcification than possible with 70 mm. photofluorograms, the majority of the patients with positive histoplasmin tests was fluoroscoped. Also, the majority of individuals with calcifications reported and who were negative to tuberculin and histoplasmin was checked by fluoroscopy; but in 12 individuals included in the group of 26 we were unable to obtain this study, hence they were listed under the roentgen diagnosis of "healed primary" which was the only method of reporting calcification in the forms used. Three students who showed minimal pulmonary infiltrates without obvious calcification were included as calcification in the charts that follow.

In addition to the students reported in these surveys we have observed several who have small pulmonary infiltrates which are indistinguishable roentgenologically from minimal pulmonary tuberculosis. These students have failed to react to 1.0 mg. O.T. but have reacted to histoplasmin. The majority gave histories of one or more previous negative tuberculin tests.

DISCUSSION

From a routine survey of 5000 students by means of photofluorograms and tuberculin testing, 160 students were found to be tuberculin negative and to have pulmonary calcifications. On 116 of these students histoplasmin tests were done. Upon review of the photofluorograms of this group we excluded 32 in whom we deemed the original diagnosis of calcification unjustified. Of the remainder, 66 were histoplasmin positive. Only three individuals in whom calcifications were shown to exist by fluoroscopic examination were negative to both histoplasmin and tuberculin skin tests.

Although Wisconsin is an area of comparatively low incidence of histoplasmin sensitivity, the general pattern of the occurrence of pulmonary calcifications is the same as for areas of higher incidence; i.e., calcification is two to four times as frequent in the histoplasmin reactor as in the tuberculin reactor (tables 1 to 4). In the composite group the incidence of pulmonary calcifications was 38.3 per cent in the histoplasmin sensitive group and 9.2 per cent in the tuberculin positive group.

The fact that histoplasmin sensitivity does not necessarily mean that the infective agent is *Histoplasma capsulatum* is well recognized. However, the high degree of correlation between histoplasmin reactions and pulmonary calcification suggests that these calcifications are the result of previous infections with *Histoplasma capsulatum* or a very closely related fungus.

TABLE I

Wisconsin Residents, June 1946 (381 students)

	H+ T-	H+ T+	T+ H-	T- H-
Calcification	7	5	10	4
No calcification	21	7	100	202
No x-ray	4	0	3	18
Total	32	12	113	224
Per cent x-rayed showing calcification	25.0	41.7	9.1	1.9

TABLE II

Non-Resident, June 1946 (184 students)

	H+ T-	H+ T+	T+ H-	T- H-
Calcification	12	12	11	5
No calcification	12	14	36	66
No x-ray	1	0	4	11
Total	25	26	51	82
Per cent x-rayed showing calcification	50.0	46.1	23.4	7.0

TABLE III

Resident and Non-Resident Women, September 1946 (1018 students)				
	H+ T-	H+ T+	T+ H-	T- H-
Calcification	12	4	7	17
No calcification	17	5	140	470
No x-ray	3	2	24	317*
Total	32	11	171	804
Per cent x-rayed showing calcification	41.4	44.4	4.8	3.4

* This large number was due to the film shortage at the time of the routine entrance examinations. In view of the negative skin tests these students were not required to report at a later date for roentgen study.

TABLE IV

All students studied				
	H+ T-	T+ H+	T+ H-	T- H-
Calcification	31	20	28	26**
No calcification	50	26	276	738
No x-ray	8	2	31	346
Total	89	48	335	1110
Per cent x-rayed showing calcification	38.3	43.5	9.2	3.4

** 12 of this group had 70 mm. film only.

In a group of 381 lifetime residents of Wisconsin the histoplasmin sensitivity was 11.5 per cent. In this group there was no significant variation in the northern and southern portions of the state, nor in the one large urban group from Milwaukee. Among the resident female students the incidence of histoplasmin reactors was much lower, 2.6 per cent. The reason for this variation is not entirely clear. However, from previous studies⁶ histoplasmin sensitivity shows substantial sex differences, especially after the age of 20, and the men were slightly older than the women in the groups which we studied.

CONCLUSION

1. Histoplasmin sensitivity among students at the University of Wisconsin reflects what is known of the geographic distribution of such sensitivity in the United States.

2. A significant proportion of hilum and pulmonary calcifications seen in chest roentgenograms is not associated with tuberculin sensitivity. In our series 66 of 73 such calcifications in tuberculin negative individuals were associated with histoplasmin sensitivity.

3. The incidence of pulmonary calcifications of the entire group surveyed in this study was 38.3 per cent in the students reacting only to histoplasmin and 9.2 per cent in those who reacted to tuberculin alone.

4. Small pulmonary infiltrates indistinguishable roentgenologically from tuberculous lesions may be associated with histoplasmin sensitivity and not tuberculin sensitivity.

5. From the roentgenologic finding of pulmonary calcifications or even infiltrations, we believe it erroneous to assume a diagnosis of tuberculous infection without further proof.

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THORACIC STOMACH PRODUCED BY ESOPHAGEAL HIATUS HERNIA AND CONGENITAL SHORT ESOPHAGUS *

By F. JOHNSON PUTNEY, M.D., *Philadelphia, Pennsylvania*

THORACIC stomach results from herniation through a normal or abnormal diaphragmatic opening, or failure of development of the esophagus. The diaphragm has only one normal opening through which gastric hernia is apt to occur and that is the esophageal passageway, considered to be the weakest point in the diaphragm. Both the vena cava and the aorta traverse the diaphragm, but the expansile vessels fill the openings so completely that herniation is prevented. Abnormal openings in the diaphragm may be produced by embryologic defects or by direct or indirect trauma. Congenital shortening of the esophagus, when present, checks the descent of the stomach into the abdominal cavity, thus giving rise to thoracic stomach.

The following table outlines the origin of thoracic stomach.

THORACIC STOMACH

1. Non-traumatic.
 - A. Through esophageal hiatus.
 - (1) Para-esophageal hernia.
 - (2) Hiatus hernia.
 - B. Congenitally short esophagus.
 - C. Through foramen of Bochdalek (pleuro-peritoneal hiatus).
 - D. Through foramen of Morgagni (anterior substernal opening).
 - E. Through congenital absence of portion of diaphragm.
2. Traumatic (direct or indirect trauma).
 - A. Through any portion of the diaphragm.

The embryonic esophagus is at first relatively short, but lengthens rapidly with the descent of the stomach. The primary longitudinal folds appear around the third month, participating at the lower end in the rotation of the stomach. Up to the second month of embryonic life the pleural and peritoneal cavities are one. The diaphragm is derived from four sources: (1) septum transversum, (2) pleuro-peritoneal membrane, (3) dorsal mesentery, and (4) from the body wall. Hernia may develop through congenital malformations of any or all of these elements, but the only types of diaphragmatic hernia that can be traced to individual sources are those involving the pleuro-peritoneal membrane and anterior substernal opening. The persistence of a dorsal opening in the diaphragm, usually on the left side, result-

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From the department of Laryngology and Broncho-Esophagology, Jefferson Hospital, Philadelphia.

ing from imperfect development of the pleuro-peritoneal membrane, leads to a type of hernia with the abdominal viscera projecting into the corresponding pleural cavity. In a few instances, protrusion of abdominal organs into the thorax occurs through a persistent anterior substernal opening (foramen of Morgagni). An intact diaphragm, weak by being locally deficient in muscle, can also provide a site for herniation into the pleural cavity, but the herniated viscera always are contained in a sacculaton of the diaphragm.

Lesions of the diaphragm in which the stomach is totally or partially displaced into the thorax through the esophageal hiatus are designated as esophageal hiatal hernias. The term, esophageal hiatal hernia, should be reserved for the type of lesion in which the stomach once was contained within the abdominal cavity and later herniated through the esophageal opening into the thorax, forming a sliding type of hernia with a covering of pleura, peritoneum or both. In herniation through the esophageal hiatus the distinction between para-esophageal hernia and true hiatus hernia is that in the former the lower end of the esophagus remains fixed in its normal position and a portion of the stomach herniates through the hiatal ring adjacent to the esophagus, while in the latter type there is protrusion of both the lower end of the esophagus and a portion of the stomach into the thorax.

The congenital short esophagus type differs from hiatal hernia in that there is not sufficient esophageal length to allow the stomach to reach the diaphragm, hence the stomach occupies its embryonic thoracic position and has never gravitated to the abdominal cavity (figure 1). The length of the esophagus affords the main difference between thoracic stomach produced by a short esophagus and herniation through the esophageal hiatus.

The incidence of thoracic stomach due either to herniation through the esophageal hiatus or to congenital short esophagus is not great, but these conditions have been recognized more frequently during the past two decades. Mention of abnormal openings in the diaphragm is found in the writings of Hippocrates, and in 1575 Paré¹ reported a case of traumatic herniation through a penetrating wound of the diaphragm. Diaphragmatic hernia was likewise described in 1761 by Morgagni² in his treatise on pathologic anatomy. In 412,149 routine chest examinations in the U. S. Army, Kinzer and Cook²² identified 38 diaphragmatic lesions, and of these 38 only three were considered from the roentgenologic standpoint to be true diaphragmatic hernias. Dwyer¹³ diagnosed but seven cases of all types of diaphragmatic hernias in 6500 gastrointestinal examinations. Over a period of five years Ritvo⁷ found 60 cases (0.75 per cent) of esophageal orifice herniation among 8000 gastrointestinal roentgenograms. Morrison⁵ observed 42 cases (1.2 per cent) of herniation through the esophageal opening in 3500 gastric cases studied. Twenty-six cases of hiatal hernia (2.1 per cent) were encountered in 1220 cases examined by Levy and Duggan.¹⁷

Most reports of large numbers of cases of diaphragmatic hernia agree that esophageal hiatal hernia is the commonest type of the non-traumatic

group. In Harrington's²³ series of 404 cases, 71 per cent of the non-traumatic group were of the esophageal hiatal type. Second in frequency was the congenitally short esophagus, comprising 8 per cent of the total number of cases. The three other sites of herniation together made up the remaining percentage. Another series of 267 cases from the Mayo Clinic by Moersch¹⁶ listed 246 (92 per cent) cases of the hiatal type in contrast to 15 traumatic and six congenital short esophagus types.



FIG. 1. Case of congenital short esophagus in an eight-year-old boy with a portion of the stomach in the thoracic cage and stenosis at the esophagogastric junction. The patient, although there was no history of swallowing a caustic previously, was considered to have a cicatricial stenosis of the esophagus, and because of marked difficulty in swallowing a gastrostomy was done. Later, esophagoscopic studies failed to reveal any injury to the esophagus, and on retrograde examination it was noted that the gastric mucosa continued well up into the chest. Appropriate radiographic studies with the patient in the right oblique position demonstrated a large portion of the stomach in the thorax with marked constriction at the esophagogastric junction.

Giffin³ was able to find references to about 650 cases of diaphragmatic hernia before 1912, and prior to 1924, Fineman and Connor⁴ could locate only five cases of congenital short esophagus in the literature. Clerf and Manges^{8, 9, 10, 11} were among the first in this country to direct attention to the congenital short esophagus, and reported 16 cases, four in children and 10 in adults. Forty-seven cases of non-traumatic esophageal hiatal hernias, 14 of which were of the short esophagus type were recorded by Polley.¹⁸ Ohler and Ritvo²⁰ observed 118 cases of hiatal hernia and 18 cases of congenital short esophagus. A report of 59 cases of thoracic stomach by Kay

and Vinson²¹ differs from most series in that the authors considered 45 were due to congenital short esophagus and the remaining 14 to an acquired paraesophageal type of hernia. Dunhill¹² published a group of 25 patients in 14 of whom the esophagus was congenitally short and 11 of whom had gastric herniation through the esophageal hiatus. Of 100 cases of diaphragmatic hernia studied by Jenkinson¹⁵ 78 per cent were acquired through the esophageal hiatus and only 5 per cent were associated with congenital shortening of the esophagus. Cowan¹⁴ reported 45 cases of thoracic stomach with 35 classed as esophageal hiatal hernias, six paraesophageal in type, and four of the short esophagus variety.

SYMPTOMS

The amount of mechanical interference with the function of the herniated viscus, the degree of diaphragmatic dysfunction, and the amount of increased intra-thoracic pressure determine the type and number of complaints. The variety of symptoms produced by hernia of the stomach through the esophageal opening and congenital short esophagus makes the clinical diagnosis difficult and, if dependency is placed on subjective manifestations, one may be easily misled. Instead of the many symptoms that commonly are present, there may be no complaints at all. Congenital short esophagus, hiatal hernia and paraesophageal hernia give rise to similar complaints, irrespective of the type present. The complaints may suggest peptic ulcer, coronary occlusion, cardiospasm, intestinal obstruction or gall stones. In Ohler and Ritvo's²⁰ series of 104 uncomplicated cases, 59 presented predominantly gastrointestinal symptoms, 23 suggested gall-bladder disease, 13 simulated coronary disease and nine were asymptomatic. Substernal pain and epigastric distress were found frequently in Jones'¹⁹ series of 128 cases.

In my experience, dysphagia of some degree is the most frequent complaint and may be accompanied by anorexia, nausea, vomiting or regurgitation. Difficulty usually occurs on eating solid foods and lodgment of food not infrequently results, so that the patients find it necessary to take large quantities of fluids with meals. Regurgitation is prone to occur after food intake and may interrupt the course of a meal.

"Food Fear" is an important symptom because the patient fears the initiation of an attack of epigastric discomfort. The subsequent restriction of diet with vomiting results in weight loss. Emaciation is particularly noticeable in children with congenital short esophagus. Small amounts of food taken at frequent intervals seem to bring about relief of the distress. In mild forms of thoracic stomach the patient may go through life with what he terms "indigestion," always being careful to eat simple foods sparingly.

Pain, either precordial or radiating upward into the shoulder or downward into the abdomen, is sometimes the first symptom. This radiating chest pain with palpitation and rapid pulse usually comes on during or after

a heavy meal and can be relieved by belching of gas or vomiting. However, relief by belching or vomiting is rarely accomplished because the pressure of the herniated viscus on the lower end of the esophagus interferes with eructation and regurgitation. Spasm of the diaphragm produces phrenic pain referred to the top of the shoulder.

In marked degrees of thoracic stomach increased intra-thoracic pressure and interference with diaphragmatic motion causes cardiac embarrassment and dyspnea. Aggravation of the symptoms takes place when the patient is prone, and breathing becomes easier in the erect position. The epigastric distress varies from a few minutes to hours with a corresponding inconstancy in the time interval. In the beginning, the attacks are usually mild and spaced at infrequent intervals, but, as the stomach becomes fixed by adhesions in the thorax, the attacks become more constant and more severe.

Hemorrhage due to ulceration occurs at times, though seldom does it become copious or alarming. Bleeding is more apt to be present in cases of congenital short esophagus than acquired hiatal hernia.

ROENTGEN FINDINGS

Roentgen examination, using an opaque material, is needed to make a diagnosis of thoracic stomach. The entire esophagus is filled to outline its course, length, width and relation with the stomach. Exact determination of the esophagogastric junction is an integral part of the examination. When an abnormality of the lower end of the esophagus is demonstrable, the esophagus and the stomach must be viewed from many angles to determine the position of the lower end of the esophagus, for it may lie behind or to one side of the stomach. The gas bubble below the diaphragm is frequently absent with the patient erect, and use of the recumbent position may be necessary to outline the fundus of the stomach and lower esophagus. Usually the portion of the stomach located in the thorax is wider than the esophagus and is best seen with the patient in the right oblique prone position, for in this position the contrast mixture can be kept in the cardia by gravity. The hiatus appears above the position that the lower end of the esophagus would normally occupy. The "pinchcock" appearance at the hiatus is absent, but the esophagogastric junction can usually be distinguished, even though, as sometimes occurs in cases of cardioesophageal relaxation, it appears only as a slight indentation in the barium column. More often some degree of narrowing at the esophagogastric junction is observed. When gastric rugae can be demonstrated above the diaphragm the diagnosis of thoracic stomach is obvious. The diagnosis of congenitally short esophagus must be established by (1) a portion of the stomach shown to stay above the diaphragm in all positions, and (2) the esophagus being too short to reach the diaphragm.

In acquired hernia through the esophageal hiatus the stomach may assume a thoracic position solely when in a recumbent position. The esoph-

agus can be shown to reach the level of the diaphragm with the herniated stomach extending along the course of the esophagus into the chest cavity. When both the lower end of the esophagus and a portion of the stomach are above the diaphragm level little difficulty in recognition is encountered.

Simple relaxation of the lower end of the esophagus has been observed infrequently but may represent the first step in the formation of a hiatal hernia (figure 2). It probably results from weakening of the muscle fibers about the hiatus. Every case in which relaxation is found should be considered a potential case of hiatal hernia.



FIG. 2. Roentgenogram made in the case of a woman, 31 years of age, who for several years had indefinite symptoms referable to the epigastrium. She had been examined in gastroenterological clinics and radiographic studies were reported normal. The symptoms, which were described mainly as "indigestion" and often manifested themselves when the patient was prone, suggested hiatal hernia. No herniation could be demonstrated by roentgen examination with the patient in the right oblique prone posture, but it was noted that the hiatal orifice always remained open as shown on the roentgenogram. The case, therefore, was considered to be one of cardioesophageal relaxation, possibly an early stage of hiatal hernia. At esophagoscopy, the only abnormality noted was failure of the hiatus to close. With the tip of the esophagoscope near the site of the hiatus esophagus, one could look directly into the stomach during inspiration, indicating that there was incompetency of the diaphragmatic sphincter.

Eventration of the diaphragm lacks these findings present in hiatal hernia: appearance of lung tissue through the gas bubble in the chest, demonstration of abdominal viscera above the diaphragm, normal diaphragmatic movement, and characteristic dome shape of the diaphragm.

ESOPHAGOSCOPY

At esophagoscopy, narrowing at the esophagogastric junction is frequently observed. The stenosis varies, commonly consisting of a funnel-like

narrowing, although an abrupt constriction or weblike stenosis may be noted. Differentiation from cicatricial changes following healing of esophagogastric ulcerations from other causes must be made. The lumen is usually concentrically placed, but no visible scarring like that seen in acquired strictures is present. Indications that the constriction is not of sphincteric or pinch-cock origin are obtained from the appearance of the narrowing, which does not resemble the normal tightening at the hiatus esophagus, and from the



FIG. 3. Small hiatal hernia occurring in a woman, age 46 years. There was no esophagoscopy evidence of stenosis at the esophagogastric junction, and no ulceration was observed.

resistance offered to the tip of the esophagoscope. Evidences of a moderate degree of chronic esophagitis and some dilatation of the thoracic esophagus may be observed.

Ulcerations varying from a small area at the point of stenosis to extensive change covering the entire stenotic lesion are sometimes found. The ulcerations are superficial, covered by a thin grayish exudate, and separated from the normal mucosa by a narrow inflammatory zone. Granulations, when present, are usually flat, and do not project greatly into the lumen. Occasionally, when neither stenosis nor ulceration at the esophagogastric junction is present the roentgen findings must be relied upon entirely for diagnosis (figure 3).

It is necessary to pass the esophagoscope into the stomach to render an opinion regarding the presence or absence of a thoracic stomach. After passing the esophagoscope through the thoracic portion of the stomach, it is not possible to demonstrate any narrowing of the stomach at the level of the diaphragm. When the esophagogastric constriction is marked, difficulty often is encountered, and endoscopic dilatation may be needed before the stomach can be visualized. After passing the stenosis, inspection of the food passageway below that point, anatomic localization of the junction of stomach and esophagus, and the absence of the normal hiatal sphincteric action afford evidence of the presence of the stomach in the thorax. In

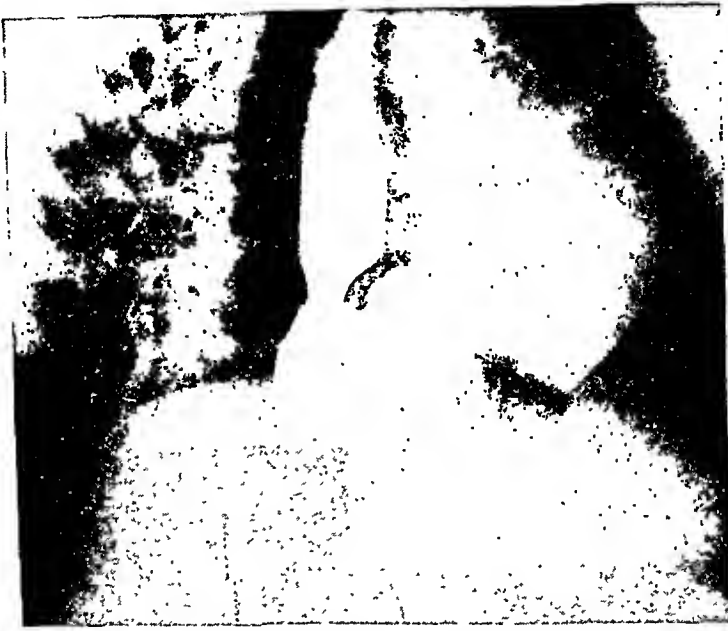


FIG. 4. Large hiatal hernia observed in a woman 67 years of age. The entire esophagus appeared greatly dilated, but this might have been the result of shortening of the esophagus itself. While the roentgen film exhibited no narrowing at the esophagogastric junction, at esophagoscopy there was a marked redundancy of folds in this locality making it difficult to introduce the esophagoscope into the stomach. Roentgenograms revealed not only marked widening of the esophageal lumen and displacement of a great part of the stomach into the thorax but also very marked dilatation of the opening in the diaphragm.

herniation through the esophageal opening redundant folds at the lower end of the esophagus are oftentimes seen and may hinder passage of the esophagoscope through the hiatus (figure 4). In cases of congenital short esophagus, immediately upon traversing the stenosis the esophagoscope enters the stomach proximal to the diaphragmatic level. Actual measurements taken from the upper alveolar margin or projection externally on the chest wall, using an applicator to localize the stenosis in relation to the epigastrium, confirm the location of the distal end of the tube. Clerf has demonstrated by retrograde esophagoscopy through a gastrostomy fistula the higher level of the esophagogastric junction in congenital short esophagus. Histologic corroboration of the presence of gastric mucosa above the diaphragmatic level

has been obtained by biopsy. For accurate localization of the anatomic site of biopsy, the tip of the esophagoscope was visualized above the diaphragm on the double plane fluoroscopic table.

In cardiospasm, no constriction at the esophagogastric junction is met with, and transition from esophagus to stomach takes place without noticeable narrowing of the passageway. In this condition, one meets gastric folds abruptly with no stenosis, ulceration, or resistance present.

At times a malignant neoplasm of the lower end of the esophagus is confused with hiatal hernia. If the ulceration is extensive and the stenosis marked, the differentiation may be difficult from esophagoscopy findings alone. The proliferating, cauliflower type of carcinoma can readily be recognized. When any doubt exists, biopsy of the ulcerated lesion is indispensable in arriving at the diagnosis.

Diverticulum of the lower end of the esophagus presents no particular difficulty in diagnosis if the opening and neck of the sac can be visualized.

TREATMENT

Treatment of thoracic stomach is directed toward two ends: namely, provision of an adequate passageway and relief of distressing symptoms. In planning therapy consideration should be given to four methods: (1) dietetic, (2) medical, (3) mechanical, and (4) surgical.

In many cases proper diet and mastication of food affords relief, and bland low residue diets are indicated. Avoidance of bulky foods, thorough chewing and swallowing small amounts at a time are helpful, for aggravation of symptoms usually follows a heavy or large meal. Liquids taken during the course of a meal aid in washing down the bolus of food, particularly if there is a tendency for stagnation to occur at the site of herniation or stenosis. Care should be taken to avoid constrictions about the abdomen for these tend to increase the intra-abdominal pressure and intensify the symptoms.

Postural measures should also be advocated to encourage the passage of food, the patient finding relief in sleeping in a semi-recumbent position, and, according to many authors, this position should be practiced routinely by these patients. Reclining after eating may be detrimental, and if a sensation of fullness is noticed, the patient is relieved by assuming the erect position.

Antispasmodics and alkalis can be utilized to advantage for relief of symptoms. Sodium bicarbonate, aluminum hydroxide, phenobarbital or belladonna are most often employed and are more effective when ulcerations are present. By counteracting the gastric acidity present in the lower end of the esophagus, relief of pain is obtained. Alkalis may be taken before or after meals following the approved peptic ulcer regime.

The principles involved in mechanical treatment are relief of obstruction by dilatation and treatment of ulcerations by topical applications. Prompt relief can be afforded by endoscopic procedures, and patients may be carried along by this means for many years, requiring treatment only two or three

times a year (figure 5). Dilatation of obstruction can be done either esophagoscopically or perorally by passage of olive-tipped bougies over a previously swallowed string. Esophagoscopic dilatation is accomplished by passage of bougies through the stenosis and, if possible, threading the esophagoscope over the bougie. When the chief difficulty is obstruction



FIG. 5. Case of a man 72 years of age who for two years had some disturbance in swallowing. Recently, substernal pain radiating through to the back developed and distressed the patient most while he was lying down. The radiographic findings are not unlike those of congenital short esophagus with a portion of stomach in the thoracic cage and stenosis at the esophagogastric junction. The esophagoscopic findings were dilatation of the esophagus with marked narrowing of the food passageway, the presence of superficial ulceration of the mucosa at the point of narrowing in the thorax, and the presence of gastric mucosa beyond the stenosis. This was believed to be a hiatal hernia of long duration, with ulceration at the esophagogastric junction which ultimately resulted in cicatricial changes. The patient subsists chiefly on soft foods and gets along well with three or four esophagoscopic dilatations and topical applications of silver nitrate 5 per cent to the ulcerated area annually.

alone, olive-tip bouginage over a previously swallowed string has enabled patients to maintain adequate nutrition with freedom from dysphagia for many years. The frequency of dilatation depends considerably on the type and severity of the constriction, but, on the average, dilatation is needed about every six weeks to keep the esophageal channel open.

In cases with ulceration treatment must be performed esophagoscopically so that the ulcerated areas may receive local treatment. Often the ulcera-

tions are persistent, requiring frequent treatments. Care should be taken not to employ too strong an alkali or acid for fear of producing more contracture and stenosis with healing of the ulceration. The use of silver nitrate in 10 per cent solution has proved adequate in promoting healing. After healing has occurred, ulcerations sometimes return with dietary indiscretions or failure to observe simple medical principles, and it may then be necessary to resume mechanical and topical treatments.

When patients obtain relief of symptoms by mechanical methods they may prefer this means of treatment. Even in the majority of congenital lesions improvement can be obtained. After a trial of dietetic, medical and mechanical measures with little or no improvement, surgical procedures should be contemplated.

The more conservative methods of therapy attempt to alleviate the symptoms and need to be continued for a long time while surgery aims at replacing the stomach in the abdomen with repair of the relaxed hiatal ring. The surgical treatment of thoracic stomach originating through the esophageal hiatus includes phrenic exeresis and surgical repair of the diaphragmatic opening, either singly or in combination. Phrenic exeresis alone provides symptomatic relief in certain cases. The indications for one or both of these surgical procedures have been outlined by Harrington.²³ The surgical approach may be either transthoracic, abdominal, or a combination of both. Not every patient is suitable for surgical treatment, and some patients improve so readily under the other methods of treatment that the risks involved in any major surgical procedure are not warranted. Cures by surgery are the rule rather than the exception in herniation through the esophageal orifice, but it is rarely possible to place the stomach in the abdominal cavity in cases of congenitally short esophagus. In 378 operated cases, Hedblom⁶ reported about 5 per cent recurrences, and, in reviewing his cases of repaired diaphragmatic hernias, Harrington²³ reported the majority of his recurrences occurred in the esophageal hiatus type of hernia.

SUMMARY

In most instances of thoracic stomach the organ gains access to the thoracic cage through the esophageal opening in the diaphragm. The abnormal position may be produced by congenital short esophagus or by one of the two types of acquired hernia through the esophageal hiatus, namely, hiatal hernia and paraesophageal hernia. The symptoms are variable and may simulate, either singly or in combination, those of gastrointestinal, cardiac, respiratory, or gall-bladder disease. The most persistent and frequent symptom is difficulty in swallowing, but occasionally absence of all symptoms occurs. Esophagoscopy together with fluoroscopic and film observations of the esophagus and stomach after the administration of an opaque material affords the only means of diagnosis. Both esophagoscopy and roentgen examinations are necessary to differentiate thoracic stomach

from other pathologic lesions at the lower end of the esophagus. Esophagoscopy also has a place in therapy, for relief may be obtained for varying periods of time by topical application to an ulcerated area and dilatation of an existing stenosis. Since this condition does not constitute a hazard to life, many patients can be carried along adequately by dietary management, medication, and mechanical treatment. If the symptoms remain refractory to these methods, surgical procedures are needed to relieve the distressing complaints.

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THE MANAGEMENT OF DESTRUCTIVE ARTHRITIS OF THE HIP BY MEANS OF INTRAVENOUS PROCAINE *

By DAVID J. GRAUBARD, M.D., JOSEPH KOVACS, M.D., and HENRY H. RITTER, M.D., *New York, N. Y.*

INTRODUCTION

DESTRUCTIVE arthritis of the hip is one of the most discouraging therapeutic problems. Many of the patients are greatly handicapped or rendered helpless and in most cases therapy thus far has been ineffective. The therapeutic approach to the disease is primarily a medical problem; however, in many cases the prevention of deformity and disability and the relief of pain are surgical procedures. Recently we reported the use of procaine intravenously in the management of arthritis and traumatic conditions.¹ This procedure often gives immediate relief of pain, loss of muscle spasm, and in some cases increased mobility. The results obtained have been encouraging.

For about one year we have observed 15 cases of destructive arthritis of the hip and have treated them with procaine intravenously. They are divided into the following categories: traumatic one case; rheumatoid four cases; osteoarthritic nine cases; Legg-Perthe's one case. They received a total of 137 procaine infusions, or an average of nine per individual.

The dosage has been calculated according to the "Procaine Unit"^{2,3}; the amount of procaine is calculated at 4 mg. per kilo body weight, dissolved in isotonic saline solution to make a 0.1 per cent solution (1-1000) to be given over a 20 minute period. For example, a 60 kilo individual receives 240 mg. of procaine in 240 c.c. of isotonic saline solution at the rate of 12 c.c. of solution per minute. The "Flowrator" is used for accurately measuring the rate of infusion.⁴

This dosage is repeated at weekly intervals, or in some instances more frequently, depending upon the severity of the pain and the general condition of the patient.

No changes in pulse rate or blood pressure have been found. Sedimentation rate and blood count studies revealed no significant changes. Blood chemistry analyses of 17 different types of blood constituents (non-protein nitrogen, urea, phosphorus, etc.) on patients receiving intravenous procaine have shown no change from normal levels.⁵

Procaine used intravenously as described is not an anesthetic but an analgesic, for at no time is the patient rendered unconscious. During the

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From the Traumatic Surgical and Medical Services of the Reconstruction Hospital Unit, New York Post-Graduate Medical School and Hospital.

Procaine Hydrochloride used was "Novocain," generously donated by the Department of Medical Research, Winthrop Stearns Inc., New York, N. Y.

administrations, about five to seven minutes after the start of the infusion, the patient feels a comfortable sense of warmth, associated with relaxation. Occasionally tearing of the eyes, metallic mouth taste, and slight lightheadedness are noted. Relief of pain and loss of spasm are noticed by the patient a few minutes after the start of the infusion. The relief of pain and the increased relaxation of muscles after the first infusion lasts from several hours to several days. Usually after the fifth or sixth weekly infusion, many have been relieved of pain and spasms for weeks, and in some cases for from four to six months.

Toxicity: The lethal dose in man is not known, and since one can not apply too rigidly the toxicity data in animals to man, the clinical experience of others served as the only guide as to the safety of intravenous procaine. It is established that the toxicity for man is dependent on the percentage concentration. To prevent untoward toxic reactions we should not exceed the "Procaine Unit" mentioned above, mix the solution thoroughly and measure accurately the rate of infusion. Only too concentrated and too fast infusion can produce severe toxic reactions as convulsions. In such a case injection of soluble barbiturates to relieve convulsions, and the use of epinephrine, oxygen and camphor for the respiratory and circulatory collapse are indicated. With our method of intravenous administration of procaine in over 2000 infusions we found neither evidence of sensitivity nor any untoward reaction. There is some evidence, however, in a further series (unpublished as yet) to suggest that the use of the drug is contraindicated in cardiac disease, especially when digitalis or digitalis-like substances are used.

None of our cases received premedication such as barbiturates. The more severe responses to this drug that we have noted on occasions and which we consider undesirable, are marked dizziness, apprehension, sensation of trembling, and sleepiness. In over 2000 administrations we had but two instances of momentary unconsciousness, but at no time was the use of sedatives, oxygen or restorative drugs necessary. Allen has given as high as 3.5 gm. for two and three-quarter hours intravenously in obstetrical cases without any mortality.⁵

Anatomy: A brief review of the blood and nerve supply of the hip and the pathology of destructive arthritis is necessary to explain the action of procaine administered intravenously.

The synovial membrane around the neck of the femur is raised into several loose longitudinal folds or retinacula in which arteries ascend to the head and supply the whole head. These vessels are derived from the obturator, medial and lateral femoral circumflex, and gluteal arteries. A small arterial supply enters the head through the ligamentum teres. The nerve supply is derived from the femoral, sciatic, and obturator nerves.

Almost all of the blood vessels entering the head of the femur reach it by way of the capsular attachments, except for the ligamentum teres. Fisher has stressed the three probable sources of supply: (1) the capillaries in the subarticular cancellous spaces which probably supply the deeper layers of cartilage cells; (2) the delicate offshoots to the lateral articular area from the *circulus vasculosus*, an arterial ring

which encircles the joint at the deflection of the synovial membrane and gives off branches to the synovial membrane; and (3) the synovial fluid upon which alone the superficial layers of the central articular area are dependent.

There is a marked distinction between the central and the lateral areas of cartilage. The central articular area possesses no perichondrium, the surface being formed of clear matrix containing no cells. The lateral area is furnished with a delicate perichondrium continuous with the synovial membrane and containing well-marked capillaries.

Pathology: It is beyond the scope of this paper to review the etiologic factors in destructive arthritis. Studies of changes of acetabular depth⁸ and variations of the angle of the femoral neck indicate that these are important factors in the development of osteoarthritis. Interference with the proper operation of the fluid mechanism as a result of variation in depth may lead to degeneration, which in turn may be accelerated by trauma, infection, or remote causes of lowered vitality. The difference in nutrition of the central and lateral portions results in the difference in their response to injury and disease.⁷ It has been suggested that there is a relationship between arteriosclerosis and osteoarthritis, since the arteries may show marked endarteritis obliterans. The disturbed circulation in arthritis may be considered an etiologic factor, and, although definite proof is lacking, it undoubtedly aggravates the arthritic condition.⁹ The interference with circulation frequently seen in trauma to the hip has produced destruction of the hip which is in many ways comparable to that seen in arthritis.^{10, 11, 12}

The initial degenerative changes appear in the cartilage: fibrillation, pitting, degeneration of cells, and increased calcification of the deeper matrix. The marginal or lateral cartilage proliferates and shows few signs characteristic of degeneration. As the central area is worn away, the bone is exposed and becomes eburnated with thickening of the subchondral plate and subjacent trabeculae by means of intramembranous ossification. The subchondral plate may or may not be thickened. The new bone formation is endochondral in origin. The normal marrow may be transposed into fat or loose fibrous tissue and in turn into osteoid tissue. The synovial membrane is invaded by fibrous tissue with increased vascularity. The chondro-osteophytes found are due to compensating proliferation of the lateral articular areas after destruction of the central areas.¹³

The characteristic eburnation in the bone is usually attributed to the attrition of opposing articular surfaces. Eventually the femoral neck penetrates the head which flattens, hypertrophies, projects around the cotyloid border, and covers the neck like a mushroom. The thickened synovial membrane hardens, ossifies in places, and often forms a bony roof extending from the upper portion of the cotyloid border; osteophytes often develop around the cavity and on the head of the femur not directly engaged in this cavity.¹⁴

The periarticular tissues often show changes difficult to explain. Wasting of surrounding muscles is often extreme and suggests an additional factor besides disuse.

Whatever the etiologic factor and course of destructive arthritis of the hip may be, we believe that a reflex vascular pattern is established at the site of inflammation, resulting in local vasospasm and capillary dysfunction, thereby interfering with normal tissue metabolism and the normal interchange of tissue fluid. Local vasospasm may hasten the degeneration and local death of tissue.² The imbalance of the autonomic nervous system produced by an irritative or toxic focus can explain many of the observations found in destructive arthritis of the hip: sensitivity to thermal changes,

atrophy of the skin, hyperhidrosis, and even flexion contractures and atrophy of muscles. It has been stated that nature's "protective muscle spasm" is the gentlest and mildest form of immobilization, since it diminishes pain by diminishing function and by putting the affected joint in the most comfortable position.¹⁸ The loss of function is primarily due to pain¹⁷; some state that the pain found in chronic inflammatory conditions is sympathetic in character.^{15, 18, 19}

Procaine administered by the intravenous route has been found to be eight times more concentrated in traumatized or inflamed tissues than in normal tissues.²⁰ The capillary permeability found in inflammatory changes allows procaine to act as a "true local anesthetic" in the affected areas. The elimination of the reflex cycle initiated by the irritative process after procaine infusion results in the diminution of vascular spasm and improvement of circulation, which is followed by the relief of pain and increased mobility.

TABLE I

Case	Age	Sex	Weight	"Procaine Unit"	Duration of Disease	No. of Injections	Results
Traumatic Case 1	45	M	70 k.	280 mg.	1 yr.	15	Relief of pain, increased mobility. Returned to work after 1 yr. disability.
Rheumatoid Case 2	41	F	60 k.	240 mg.	10 yrs.	18	Relief of pain, increased mobility, has returned to work.
Case 3	55	F	85 k.	340 mg.	12 yrs.	6	Relief of pain and increased mobility.
Case 4	38	M	60 k.	240 mg.	1 yr.	4	Temporary relief of pain and spasm.
Case 5	49	F	55 k.	220 mg.	7 yrs.	15	Relief of pain and increased mobility.
Osteoarthritis Case 6	69	M	70 k.	280 mg.	11 yrs.	16	Relief of pain and increased mobility.
Case 7	40	M	70 k.	280 mg.	11 yrs.	5	Relief of pain and spasm, has returned to work.
Case 8	47	F	85 k.	340 mg.	7 yrs.	8	Moderate relief of pain, small increase in mobility.
Case 9	72	F	52 k.	208 mg.	15 yrs.	3	Relief of pain, increased mobility, able to do housework.
Case 10	50	F	62 k.	248 mg.	2 yrs.	2	Relief of pain and increased mobility.
Case 11	67	F	70 k.	280 mg.	8 yrs.	8	Increased mobility, relief of pain, able to do housework.
Case 12	62	M	60 k.	240 mg.	5 yrs.	6	Partial relief of pain and spasm, able to do work.
Case 13	48	M	80 k.	320 mg.	3 yrs.	5	Relief of pain, increased mobility, returned to work.
Case 14	62	M	65 k.	260 mg.	8 yrs.	5	Relief of pain, increased mobility, returned to work.
Legg-Perthe's Case 15	21	F	50 k.	200 mg.	9 yrs.	21	Relief of pain and increased mobility.

CLINICAL DATA

All our cases have been treated under close supervision at the Reconstruction Hospital Unit, either as out-patients or in-patients. Complete history, physical examination and laboratory investigation were done on all. Prior to the inception of treatment with intravenous procaine, all cases had been given various other types of therapy with little or no relief of pain, and showed restricted mobility and early flexion contractures. All our patients continue under observation, and some are still being treated.

Table 1 is a summary of the cases covered by this report.

The following case reports are examples of our results:



FIG. 1. Case 1, N. V. Destructive arthritis, right hip, traumatic.

Case 1 (figure 1). N. V. is a 45 year old male, machinist, who was injured in February, 1946. For nine months he was bedridden with pain and loss of motion in the right hip. Radiographic examination showed a narrowing of the joint with partial destruction of the hip and haziness of the head of the femur. After the fifth infusion of procaine five days after admission, he was able to get out of bed symptom-free, and could walk about without the use of a cane. It is now four months since the last infusion, and, except for shortening of the right lower extremity of $\frac{1}{4}$ of an inch, he is able to walk and bend without difficulty, and has returned to work.

Case 2 (figure 2). A. S. is a 41 year old single female who has been partially disabled for the past 10 years because of rheumatoid arthritis involving not only the hips but also the elbows, shoulders, and knees. Radiographic examination showed considerable narrowing of the hip region and marked destruction of the femoral heads. The patient suffered a great deal of pain, especially in the adductor region of the thigh. Immediately following the first infusion the patient was able to get out of bed, free of pain, and was able to walk with a great deal of freedom. To date, she has received 18 infusions at weekly intervals. Her last infusion was given two months ago, at which time the patient had returned to work as a stenographer. There is still considerable limitation of motion.



FIG. 2. Case 2, A. S. Destructive arthritis, both hips, rheumatoid.

Case 5. A. S. is a 49 year old female, housewife, who has been disabled for the past seven years with rheumatoid arthritis involving hands, wrists, elbows, shoulders, hips, knees and ankles. She has been bedridden for the past four years and has been unable to move or feed herself. The extremities were held in flexion, and contractures had taken place. In the past eight weeks she has received a total of 15 infusions. She has been free of pain for the past six weeks; mobility has increased to the point where she has been able to feed herself and move about in bed without difficulty. The flexion contractures were improved considerably. All adductor pain has disappeared, and the patient has been able to stand on her feet for the first time in four years. Her roentgen-ray shows a destructive arthritis of both hips with flattening of the femoral head.



FIG. 3. Case 7. Destructive arthritis, both hips, osteoarthritic.



FIG. 4. Case 6. Destructive arthritis, left hip, osteoarthritic.

Case 7 (figure 3). J. D. is a 46 year old married male, a porter, who complained of severe pain in both hips and inability to bend. He got about with the aid of two canes on his "good days" and crutches on the others. He had been "stiff" from osteoarthritis of both hips for the past four years. Roentgenologic examination revealed marked bony excrescences at the acetabular regions to such a degree that fusion of the hip joint was believed to have taken place. His weight was 70 kilograms and he received 280 mg. of procaine beginning on September 18, 1946. He has received 12 infusions, the last having been given over six months ago. Immediately after the first infusion he had relief of pain and was able to flex the thigh on the abdomen to a 90 degree angle. The reason that this patient received so many infusions is that he



FIG. 5. Case 15. Destructive arthritis Right hip—Legg-Perthe's; Left hip—traumatic.

feared the return of pain and reported weekly. It is interesting to note that he is working as a porter in an apartment house and does not require the use of crutches or canes in getting about. At his last visit to us last month, he reported that he had gained 10 pounds.

Case 6 (figure 4). L. S. is a 69 year old male, unemployed, who has been suffering from pain and inability to move the left hip for the past 11 years. Radiographic examination revealed advanced destructive arthritic changes of the left hip with complete obliteration of joint space and advanced arteriosclerotic changes in the femoral vessels bilaterally. Immediately following the first infusion the patient was able to flex the left hip without difficulty and pain. This patient has returned for several infusions because of fear of the recurrence of pain. At his last visit to us about two months ago he was considering obtaining a position away from New York since he is able to move his hip and has been free of symptoms for such a long time.

Case 15 (figure 5). S. P. is a 21 year old single female, clerk. At the age of 12, this girl suffered from an injury of the epiphysis of the left hip, and the head of the femur was removed at another hospital. Subsequently, she developed symptoms in the opposite hip with difficulty in walking and pain. Radiographic examination revealed a flattening of the head of the femur of the right hip and absence of the head and neck on the left hip. There was marked condensation of the acetabular regions. She has received a total of 21 infusions at weekly intervals with marked relief of pain and spasm and ability to flex the thigh on abdomen with great ease. This patient is working as a stenographer and has lost no time from her work because of pain in hip. Prior to this treatment, this patient would lose three to four days per month because of pain and inability to work.

DISCUSSION

Since there is no clearly defined treatment in destructive arthritis of the hip, the individual physician must depend on symptomatic therapy in order to provide relief for the patient. Relief of pain and spasm is of prime importance. It is for this immediate relief of pain that patients seek the physician.

We are all familiar with the restricted benefits of salicylates and the failure of sulfur²¹ and vaccines.²² In one respect, there seems to be unanimity of expression that gold therapy has little or no influence on destructive arthritis of the hip. In fact, no therapy has had any influence to date on this condition.

The physical therapist can offer much in the way of relief, but here the relief is very temporary and in some instances exacerbations have been produced.

Surgically, the results have not been persistently good^{23, 24, 25} with only temporary relief of pain and spasm as the final result. All cases cannot be considered for arthroplasty.²⁶ Arthritis in the lumbar portion of the spine, bilateral hip involvement, age over 55, are all contraindications for arthroplasty.¹⁴ The simple procedure of neurectomy of the obturator nerve^{27, 28} has not produced encouraging results.²⁹ Radicotomy of the third, fourth and fifth lumbar roots is of doubtful value.³⁰ It has been stated that 50 to 60 per cent of these cases treated by the intra-articular injection of lactic acid will improve,³¹ but these figures have not been confirmed.

We know that the articular cartilage itself is insensitive and that the pain is due to secondary changes in the periarticular structure and capsule due to contracture.^{32, 33} The relief of pain and spasm by intravenous procaine enables the physician and surgeon to avoid major procedures of doubtful value. This method is not a cure of the basic etiologic factors; but, by relieving pain and spasm and by increasing mobility, in our experience this treatment obtains more persistent good results than the other methods employed.

Our patients gained increased mobility of the hip joint as signified by improved walking and stability. Some who used crutches before could

walk again without the aid of canes. Many have returned to work and regained a useful life. It is too early to say how permanent the results will be, for the longest duration of observation under this type of treatment has been one year. Yet we feel that this method so far has given the most satisfactory results in our experience in the relief of pain, relief of spasm, and increased mobility.

CONCLUSIONS

1. The use of procaine intravenously in the management of destructive arthritis of the hip is a safe hospital procedure provided the administration is controlled.

2. Relief of pain and spasm, and, in some instances, increased mobility can be effected.

3. The results in 15 cases treated by this method and followed for one year have been encouraging.

4. Intravenous procaine should be considered as an adjunct in the management of destructive arthritis of the hip.

5. Too short a period of time has elapsed and too few cases are presented for definite conclusions. This method of treatment is still in an investigative stage.

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VITAMIN E IN HEART DISEASE *

By HYMAN LEVY, M.D., and ERNST P. BOAS, M.D., *New York, N. Y.*

ENTHUSIASTIC reports^{1, 2} on the value of vitamin E (alpha-tocopherol) in the treatment of certain forms of heart disease warrant further trial with this substance. Cardiac failure has been reported in cattle fed with vitamin E-free rations.³ Such animals exhibit progressive electrocardiographic abnormalities, are prone to sudden death, and sections of their heart muscle show microscopical evidences of atrophy and scarring of muscle fibers. In our small but carefully studied and controlled group of patients, we have been unable to reproduce the therapeutic improvement previously reported. In fact, in chronic angina pectoris due to coronary sclerosis, in heart failure secondary to chronic rheumatic cardiovalvular disease, and in the so-called state of coronary insufficiency characterized by repeated anginal seizures at rest, we have found alpha-tocopherol a singularly inert drug.

MATERIAL

Thirteen patients were selected from an office practice devoted largely to the diagnosis and treatment of heart diseases. Only those were chosen who had been patients for some time, whose reactions to pain and distress were not abnormal, and in whom one might expect some degree of accuracy in appraising changes in their symptomatology. Further, patients were selected who exhibited relatively stable patterns in their symptomatology. Those with angina pectoris had shown the classical syndrome of chest pain on effort or emotion, and there had been no significant change in the pattern of the pain in the few months immediately preceding the study. Those with cardiac failure following chronic rheumatic cardiovalvular disease had permanent auricular fibrillation and had persistent heart failure of moderate degree in spite of reasonable control with digitalis and mercurial diuretics. Those with coronary insufficiency were patients in whom the anginal pattern was characterized by increased frequency and intensity of spontaneous anginal attacks, suggesting the possibility of active changes within the coronary arteries. The dosage of the drug † varied from 200 mg. to 800 mg. daily. In most of the patients, plasma levels of alpha-tocopherol were determined while the vitamin was being taken; in some, control levels were also taken before the vitamin was administered.

CASES OF CHRONIC ANGINA PECTORIS

Case 1. W. R., male, aged 57, had been under continuous observation for five years, for angina pectoris due to coronary sclerosis; chest pain was provoked on the

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From the medical service of Dr. George Baehr, Mount Sinai Hospital.

† The vitamin E preparation used was "Ephynal" and was supplied through the generosity of the Hoffmann-LaRoche Company.

slightest effort for several months. For a period of seven weeks, vitamin E in daily doses of 200 mg. was given. During the time the drug was given, the plasma level for a-tocopherol was 1.74 mg. per cent, indicative of adequate absorption. At the end of the seven week period, anginal symptoms were unchanged; the patient reported no improvement and examination disclosed no objective changes. After discontinuing the drug for four weeks, it was reinstated, this time at the daily dose level of 800 mg.; within a week the patient complained of frontal and parietal headache and stated that generally he felt worse while taking the drug. The dose was accordingly dropped to 400 mg. per day; the headache subsided; the intensity and frequency of the anginal pain were, however, unaltered. After the drug was given for two weeks at the dose of 400 mg., it was discontinued. In summary, vitamin E was administered for 10 weeks in doses varying from 200 to 800 mg. daily without affecting the pattern, the intensity, the physical findings or the course of the anginal syndrome. Frequent electrocardiograms, taken during the course of this study, showed no changes.

Case 2. H. S., male, aged 66. Coronary thrombosis had occurred in this patient eight years previously, and for the past seven years, the classical pattern of angina pectoris had been present; walking a single block caused him to halt because of pain to the left of the sternum. The anginal pain was of relative constancy, there being no recent aggravation in intensity of pain, nor development of chest pain at rest. Physical examination at the age of 65 showed no evidence of congestive failure; fluoroscopy showed much enlargement of the left ventricle and slight enlargement of the left auricle; regular sinus rhythm was present; the blood pressure was 186 mm. Hg systolic and 76 mm. diastolic. The electrocardiogram disclosed a PR interval of 0.22 second, but no other abnormality. For the first week, vitamin E in daily doses of 300 mg. was given; on this dosage the plasma level of a-tocopherol was 2.50 mg. per cent. No effect on the clinical picture was noted and the drug was increased to 600 mg. daily, and continued at this level two weeks. Again there was no effect; the anginal syndrome was unvaried. He would be stopped as he tried to walk one block. An electrocardiogram taken after the institution of vitamin E therapy disclosed no change in the PR interval. In summary three weeks of vitamin E in doses from 300 to 600 mg. daily produced no effect on the pattern of this patient's anginal pain.

Case 3. M. K., male, aged 64. At the age of 50 he suffered from midsternal heartburn, suggestive of peptic ulceration because of its post-prandial time relationships and its relief by food and alkalis; no ulcer could be demonstrated roentgenographically, however. Beginning at the age of 54, walking a block or two would provoke pain in the middle of the chest, compelling him to rest; often the pain would radiate to both arms and be associated with numbness of the finger tips. Nitroglycerine afforded prompt relief. Fluoroscopy of the heart was normal; the electrocardiogram was normal; the rhythm was regular and the heart sounds were of good quality. For a period of seven weeks, 200 mg. of vitamin E were given daily. Aside from the development of slight constipation while taking the drug, no effects were noted either by the patient or by us. During this period, the plasma concentration of a-tocopherol was 1.95 mg. per cent. For the next 10 days, the dose was increased to 600 mg. daily; on this, the plasma level for a-tocopherol was 2.51 mg. per cent. As no change in the clinical picture was found, the drug was stopped and for the next seven weeks no vitamin E was administered. The clinical manifestations of the coronary disease were unaltered and vitamin E was again started, at the same level of dosage, 600 mg. per day, and continued for the next two weeks. The drug was finally stopped after 11 weeks of intermittent administration. The only change was the constipation already noted. The patient continued to show the same kind of variation in his symptomatology, related to weather changes and the state of fullness of his stomach, variations which had been present for 13 years and which were unaffected by the administration of vitamin E.

Case 4. S. F., male, aged 68; had been under our constant care and supervision for 16 years. He had chronic rheumatic cardiovalvular disease with aortic stenosis and insufficiency and electrocardiographic evidences of myocardial damage. Moderate cardiac enlargement and hypertension were also present. At the age of 66, he was troubled with stubborn angina pectoris, provoked by slight effort and by walking a block, compelling him to halt. His consumption of nitroglycerine was about 75 tablets per week. A year later, at the age of 67, the clinical picture was much the same, that is chest pain readily provoked by the slightest effort. Control plasma level of α -tocopherol was 0.90 mg. per cent. He was given 200 mg. vitamin E daily for a total period of seven weeks. At the end of this time no improvement was recorded; the pain came as frequently, although during the time vitamin E was prescribed, he believed the pain was less intense. The anginal pain was provoked as readily as before. Finally he was subjected to paravertebral block with alcohol, with poor results. He remains in chronic heart failure which followed the block within one week.

Case 5. M. S., male, aged 49; under continuous observation for stubborn angina pectoris on any effort, beginning seven years previously, and not responding to paravertebral block with alcohol. There was no hypertension, cardiac enlargement or heart failure. He was given 200 mg. vitamin E daily for a period of six weeks. Plasma concentration of α -tocopherol while on the drug was 1.17 mg. per cent. He felt worse generally while on the drug. The anginal pattern was altogether unchanged. Physical examination at regular intervals including electrocardiography did not reveal any alteration.

CASES OF ACTIVE ANGINA PECTORIS

Case 6. C. F., female, aged 49. This patient had had marked hypertension for 14 years, the blood pressure ranging up to 240/140; there was slight enlargement of the left ventricle and electrocardiographic evidences of left ventricular strain. She had had classical anginal pain on effort. Beginning in August 1946, attacks of chest pain became more and more frequent, occurring several times each day, at rest. On one single day, attacks occurred with increasing frequency and intensity, requiring nitroglycerine at every turn, and the clinical picture suggested the imminence of a myocardial infarction. She was therefore hospitalized for several weeks; the attacks persisted while at rest in the hospital, although they were less frequent. There were no electrocardiographic or other evidences of myocardial necrosis. After discharge from the hospital, attacks of lower anterior chest pain radiating to both upper extremities persisted, and she required about 20 nitroglycerine tablets daily for the periodic relief of pain. On November 8, 1946 vitamin E was started, 700 mg. daily. Her reaction to the drug consisted of vertigo in addition to constipation. On November 18, the dose was reduced to 300 mg. daily; one week later, the plasma level for α -tocopherol was 4.26 mg. per cent. On this lowered dosage, vertigo decreased, although some degree of dizziness persisted. During the week of November 18 to 25 anginal attacks did not reappear; she felt poorly, however, due to the dizziness and headache; weakness was so pronounced that she found it difficult to walk outside. The drug was now stopped. During the ensuing three weeks without the drug, there were alternate periods of pain and free intervals of several days each. She believed that this alternation was of about the same degree, both on and off the drug, and she preferred not to continue the use of the vitamin E. In all she had the drug for three weeks, the dose ranging from 300 to 700 mg. daily. The absorption of the drug was excellent as evidenced by the unusually high reading of 4.26 mg. per cent. When she was last seen, in April, 1947, she continued to complain of weakness and the inability to walk more than one block. There has been no change in the physical examination and the electrocardiogram has shown very minor alterations in the T-wave of the precordial leads without the development of Q-waves. There has been no febrile

reaction or significant change in the sedimentation of the red blood cells to indicate definite myocardial necrosis.

Case 7. L. C., male, aged 51. Four years previously, in 1942, he suffered from acute glomerulo-nephritis, following a sore throat. During the active infection there was cardiac failure, moderate cardiac enlargement, good heart tones and a normal electrocardiogram. In July, 1946, he suffered a severe attack of precordial pain radiating to the left arm. Following this episode, he would be stopped, after walking half a block, by constricting chest pain. Electrocardiogram now showed a diphasic T-wave in the precordial lead CF5. In September, 1946, further electrocardiographic changes were seen; the T-waves in Leads I and II were flat and the T-wave in Lead IV was inverted. In October, 1946, when he complained of very frequent attacks of chest pain requiring many nitroglycerine tablets, and when the increasing frequency and intensity of attacks, often occurring at rest, suggested the possibility of impending myocardial infarction, the patient was given 200 mg. of vitamin E daily. After three weeks, there was no relief, the pattern and frequency of the anginal seizures being unaltered. Good absorption of the drug was indicated by a plasma level of 3.0 mg. per cent. When he had taken the vitamin for four weeks at a daily dose of 200 mg., he was then given 800 mg. daily. Within a few days he complained of dizziness, the angina became worse, and so he voluntarily stopped the drug. In May, 1947, he reported that the attacks of anginal pain had persisted throughout the winter, and required the free use of nitroglycerine.

Case 8. J. W., male, aged 57; has been under our continuous observation for 11 years. At the age of 46, he first noted chest pain radiating to both hands on walking in the morning and compelling him to halt. One week after the onset of the angina pectoris, he suffered a severe attack of chest pain. On examination shortly after this episode, the important physical findings were dull heart sounds, slight enlargement of the left ventricle, a blood pressure of 110/70, and some slurring of the QRS complexes in the electrocardiogram. Three years later at the age of 49, for a period of about three months, he complained of frequent spontaneous attacks of chest pain. The electrocardiogram remained unaltered. Seven years later at the age of 56, there was a recurrence of the frequent and spontaneous attacks of chest pain. Because of the state of coronary insufficiency, vitamin E was given. The control level for α -tocopherol was 1.68 mg. per cent. Initial dosage was 200 mg. daily; at the end of two weeks, he reported that he felt better during this two week period, walked more freely, up to three blocks, where formerly he had been stopped after walking half a block. He found, too, that he was using much less nitroglycerine. The plasma level on this dosage was 2.16 mg. per cent. Physical examination including electrocardiogram showed no significant change. The improvement continued through the succeeding two weeks, when the dose was kept at the same level, 200 mg. daily. After taking the drug for six weeks, he was able to report that he had moderate relief from the anginal attacks, both in their frequency and intensity. Within two days after stopping the vitamin E, he reported that the angina was worse. After a free interval of 11 days, without the drug, it was again dispensed, 200 mg. daily for a period of two weeks; during this period, however, the pain was again more persistent and he had to have recourse again to the very frequent use of nitroglycerine. Up to this point, he had had 10 weeks of intermittent administration of the drug; there was some subjective improvement in the first two weeks, but this relief was only temporary. Next he was given erythrol tetranitrate for a week, without any noticeable change. After a period of four weeks without any drugs, vitamin E was again administered, this time 800 mg. daily. Aside from slight epigastric distress, he reported no change. The blood level on this dosage was 3.45 mg. per cent. During the next week the patient took from 300 to 400 mg. daily and noted the same frequency of anginal pain and the same frequency of resort to nitroglycerine. For the final week, of a total of

12 weeks, he took 400 mg. daily of vitamin E and found that he was compelled to take about 12 nitroglycerine tablets daily, roughly the maximum amount he was accustomed to require for the day. Finally, some eight months after vitamin E was first tried, he developed abdominal distress preceding the attacks of chest pain and this change in pattern of the pain was associated with slight fever and alterations in the electrocardiogram indicative of some degree of myocardial necrosis. The accelerated sedimentation rate of the red blood cells added further support to this conclusion. Following this, a bed rest period of two weeks found him more comfortable.

CHRONIC HEART FAILURE SECONDARY TO MYOCARDIAL INFARCTION

Case 9. J. A., male, aged 58. In April, 1946 he suffered a myocardial infarction, very possibly induced by insulin, to which he was sensitive. He returned to work in September, 1946, but after a month was compelled to give it up because of increasing fatigue and edema, progressing to frank heart failure in November, 1946. Examination at this time disclosed marked dyspnea at rest, basal pulmonary congestion, enlarged tender liver, and pitting edema of the legs. The electrocardiogram showed prominent Q-waves in Leads II, III and IV. On digitalis and periodic injections of mercurial diuretics, improvement was noticeable but some degree of heart failure persisted, and required the continued use of mercurial diuretics. To determine what effect if any vitamin E might have on the failing myocardium, he was started on vitamin E, 200 mg. daily on February 1, 1947. Two weeks later he reported no improvement, and the physical examination was unchanged; the degree of pulmonary congestion and hepatic distention were unaltered. The plasma level of a-tocopherol on this dosage was 1.95 mg. per cent. The drug was now increased to 400 mg. daily, and 10 days later there was still no sign of improvement. The increased dosage was reflected in a higher plasma level of a-tocopherol, 3.24 mg. per cent. In all, he had taken the drug for five and one-half weeks, at dosages from 200 to 400 mg. daily. He then was placed on a low salt diet, containing about 1.5 grams of salt per day. He was next seen five weeks later when he exhibited a striking change; he felt and looked better. The last mercurial diuretic had been given two weeks previously and he did not feel the need for another injection at this visit. Formerly he had been accustomed to taking the mercurial injection at weekly intervals. Physical examination corroborated the patient's estimate of his improvement; the lungs were clear; the liver smaller and less tense.

CHRONIC HEART FAILURE DUE TO CHRONIC RHEUMATIC CARDIOVALVULAR DISEASES

Case 10. S. G., female, aged 56. A cardiac murmur has been present since the age of 41, although there is no history of rheumatic fever. At the age of 45 she began to complain of dyspnea and palpitation; these symptoms became worse at the age of 52. Examination at this time disclosed much generalized enlargement of the heart, the murmur of mitral insufficiency and the sharp first sound of mitral stenosis, and auricular fibrillation. The liver was enlarged to two fingers'-breadth below the costal margin. She did relatively well for the next two years, but at the age of 55, progressive weakness and edema appeared and despite frequent mercurial diuretics, evidences of heart failure remained. Control reading of a-tocopherol in the plasma was 1.38 mg. per cent. For the first week, the dosage of vitamin E was 200 mg. daily, with a corresponding increase of the plasma level to 3.09 mg. per cent. There was no evidence of diuresis or other improvement. For the second week, the dose was raised to 400 mg. daily. The only change noted by the patient was increase in appetite; the dyspnea was more marked, the liver was greatly distended. In the third week, she took 600 mg. daily; again, except for increase in appetite, of coronary in-

sufficiency, characterized by a new pattern of increased frequency and intensity of attacks, often occurring at complete rest, there was no change to be attributed to the use of this vitamin.

In conclusion, we find no clinical evidence to warrant the use of vitamin E in the types of heart disease discussed.

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STUDIES ON EXPERIMENTAL PHOSGENE POISONING V. INFUSIONS IN THE TREATMENT OF EXPERI- MENTAL PHOSGENE POISONING *

By H. D. BRUNER, M.D., PH.D., MARY H. GIBBON, MILES D. MCCARTHY,
PH.D., ROBERT D. BOCHE, PH.D., TIMOTHY R. TALBOT, JR., M.D.,†
JOHN S. LOCKWOOD, M.D., and GEORGE B. SANDERS, M.D.,
Philadelphia, Pennsylvania

FOLLOWING exposure to phosgene, the transudation of *plasma* into the pulmonary alveoli leads to two functional derangements, either of which is potentially lethal.^{1, 2, 3} One is the obstruction to pulmonary gaseous exchange due to the physical presence of this fluid in the alveoli and eventually in the bronchioles; the development and magnitude of this lesion can be evaluated by observing the arterial oxygen saturation. The second is loss of circulating plasma volume which results in a hemodynamic state very similar to secondary or surgical shock. The accompanying hemoconcentration may be so extreme that the raised blood viscosity seriously impedes flow in whatever capillaries are receiving blood,⁴ but the increased oxygen capacity tends to compensate. The progress of this defect can be estimated by the decline of venous oxygen saturation. Thus the former lesion produces an anoxic anoxia, and the latter a stagnant anoxia. Either form of anoxia alone is capable of causing death of tissues, but combined, as they are in phosgene and other types of irritant gas poisoning, they seem to exert a mutually potentiating effect on each other. The steady downward course of arterial and venous oxygen saturations is clearly evident in Underhill's⁵ data on lethally poisoned dogs. When serial blood gas analyses are impractical, serial hematocrit determinations offer the best means of following the rate and degree of plasma loss into the lung; however, the administration of fluids may lead to an erroneous deduction.

As shown in table I, the pathologic physiology of phosgene poisoning may be represented as a compound vicious cycle; each of the two component cycles tends to magnify the other, even if loss of plasma into the lungs ceases. Obviously therapy should be directed toward breaking into and reversing not one but both vicious cycles. The ideal therapy would obviously consist of the restoration of normal permeability of the capillaries, but no regimen or agent is now known which will accomplish this, once the toxic agent has

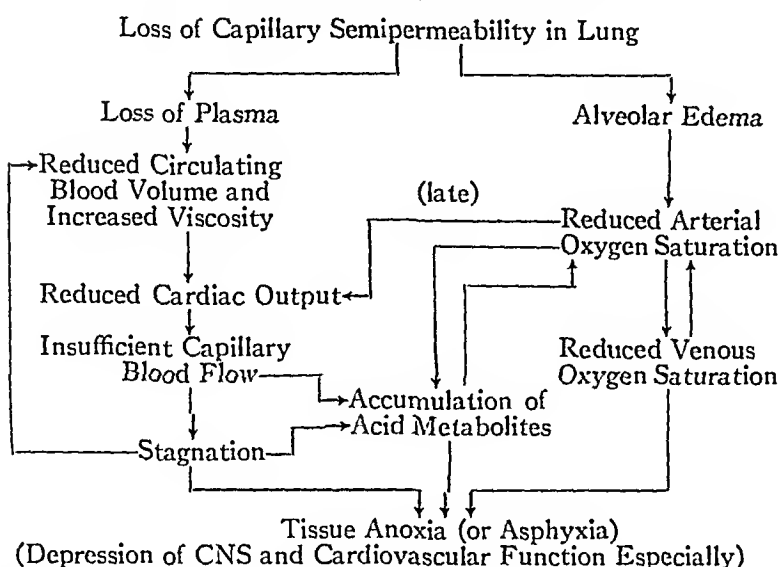
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From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania, Philadelphia.

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† Formerly Lieut. (MC), U.S.N.R. The Bureau of Medicine and Surgery, U. S. Navy, does not necessarily endorse the views or opinions which are expressed in this paper.

TABLE I
Showing the Probable Sequence of Abnormal Physiological Changes in Experimental Phosgene Poisoning*



* The rabbit, a "wet" animal, shows little or no hemoconcentration, and hence the left hand cycle is presumed not to be present in that species.

damaged them. In experimental animals and human casualties which survive, hemoconcentration reaches its peak and reverses between 15 and 35 hours after gassing; the reversal is taken to mean spontaneous restoration of an effective degree of normal permeability, but the mechanisms which bring this about are unknown.

Attempted treatment of the anoxic anoxia in phosgene-poisoned dogs by oxygen therapy alone was not successful: The best result obtained by continuous 95 per cent therapy was prolongation of survival in the acute stage of the edema; ultimate survival rate, the real criterion of benefit, was not improved.⁶ In addition, 95 per cent oxygen therapy combined with pressure breathing on inspiration, or on expiration, was maintained for 36 hours after gassing without benefit.⁷

Since treatment of the stagnant anoxia is essentially treatment of the shock-like state of the circulation, trials of the accepted therapy for secondary shock were carried out with the results described in this report. As there was little or no evidence of erythrocyte loss, restoration of the circulating plasma volume was the primary objective. Because the venous oxygen saturation rose following saline infusion in certain data of Underhill's experiments,⁵ there was reason to anticipate at least some control of the stagnant anoxia.

METHODS

The dogs used in these experiments were healthy adult mongrels, free of respiratory infection. They were exposed to phosgene in pairs or in fours in a large chamber operated dynamically by technics previously de-

scribed.¹ As it had been found that concentration of phosgene and duration of exposure could be varied reciprocally without affecting the course of the poisoning or the findings at autopsy, both the long duration-low concentration and the high concentration-short duration types of exposure were used. Half of the gassed animals became simultaneous toxicity controls by lottery. Details of the various treatments employed are given below in their respective sections. The control dogs were subjected to the same procedures as the treated animals with the exception of infusions; following treatment, all dogs were kept under observation until death or recovery. The animals that died were autopsied at once, or stored overnight in a refrigerator at 4° C. Food and water were available to the animals at all times, but both were usually refused for the first 36 hours after gassing.

RESULTS

The results are separated in relation to the different types of infusions used:

A. Concentrated Plasma. Under sterile precautions blood from a number of donor dogs was pooled in citrate, centrifuged and the plasma dried from the frozen state. Shortly before use it was dissolved in one-fourth its original volume of sterile distilled water and filtered to remove any insoluble material. This 4N concentrated plasma was administered to seven dogs gassed by an L(CT)99 of phosgene. When severe edema had developed, four dogs received the concentrated plasma in amounts equal to one-fourth the estimated plasma loss, as calculated from the hematocrit change. Two other dogs received 4N plasma in three doses at one to two hour intervals, the total amounts being one eighth the estimated original plasma volume. Despite such treatment hemoconcentration was not controlled. The animals, especially when edema was marked, reacted unfavorably; respiratory distress was accentuated. The average lung/body weight ratios at death were higher than those of the control dogs, or of dogs treated with equal relative volumes of saline. At autopsy the edema fluid seemed unusually viscous and the froth in the air passages was stiff; the protein content of the fluid was as high or higher than the original plasma protein content. The seventh dog received a total of 90 c.c. of 4N plasma, the equivalent of his original plasma volume, without effect on the hemoconcentration.

At this time data were received from England of investigations, subsequently published,^{2,8} which paralleled in purpose, technic and results the work above. These data clearly demonstrated that plasma infusions were valueless, if not actually deleterious in phosgene poisoning; not only did the plasma infusions fail materially to affect the hemoconcentration, they exaggerated the anoxic symptoms.

B. Pectin Solution. A buffered pectin solution* was used as a prototype of non-nitrogenous plasma substitutes. Because it has a long slender

* Supplied through the generosity of Dr. Richard Johnson, of Frederick Stearns & Co. (Lat. P C No. 1).

molecular, or micellar configuration, it seemed possible that it might occlude the capillary defects through which the plasma proteins passed so readily. The substance was given a trial in six dogs poisoned by an L(CT)99 of phosgene. Total quantities of 40 to 190 c.c. in divided doses were infused at intervals of two to four hours, or in a single dose at 10 hours after gassing. The infusions partially controlled hemoconcentration and appeared to have no adverse effects, but they did not lengthen survival or prevent death. Since approximately equal amounts of pectin⁹ were found in plasma and in the edema fluid at death, pectin offered no advantage over plasma.

C. Gelatin Solution. Infusion of a buffered gelatin solution which has been used clinically¹⁰ was combined with sedation and oxygen therapy in an effort to duplicate the clinical management of irritant gas poisoning. Thirteen dogs poisoned by an L(CT)60-70 of phosgene received 2.2 mg. of morphine sulfate and 2 c.c. of 50 per cent ether in peanut oil (as a bronchodilator) intramuscularly every four hours. One hundred per cent oxygen by mask was given as required on the basis of cyanosis of the mucous membranes. The gelatin solution contained sodium succinate in a concentration of 2 per cent¹¹; this addition did not disturb the solubility, pH or osmotic properties of the gelatin. The quantity of gelatin slowly infused every two hours intravenously was calculated from the change of the hematocrit reading from normal, assuming a blood volume of 90 c.c. per kg. body weight; the indicated loss at each period was given, regardless of the volumes previously administered. This treatment was continued for 36 hours under constant individual nursing for each animal.

This treatment slightly prolonged the average length of survival of dogs dying acutely, compared with that of the controls, but the average mortality of the treated dogs was 22 per cent greater at 10 days; the average lung/body weight ratios of the treated dogs were unusually high. The edema fluid and the lungs solidified on cooling, indicating that the gelatin had entered the edema fluid in appreciable amounts, despite its highly asymmetrical molecule.¹² As with the concentrated plasma, infusion of gelatin when edema was marked resulted in exacerbation of the respiratory difficulty within the following hour. At this stage even large infusions of gelatin failed to control the progress of hemoconcentration.

D. Saline Solution. Because the solutions with high molecular weight exaggerated the pulmonary symptoms, the effects of a non-viscous saline solution were studied. A modified Ringer's solution ($\text{NaCl} = 0.92$ per cent; $\text{CaCl}_2 = 0.125$ per cent; $\text{KCl} = 0.042$ per cent) was administered by continuous intravenous drip technic to 46 dogs during the first five and one-half to seven hours following exposure to an L(CT)60-70 of phosgene. This solution contained five times the usual concentration of calcium; this use of calcium was suggested by data from another laboratory.¹³ The total amount of fluid infused, 30 c.c. per kg., is approximately 60 per cent of the total estimated plasma volume and roughly equivalent to the usual increment of lung weight in fatal cases of edema.

TABLE II

The Effect of Calcium-Fortified Ringer's Solution (30 c.c./Kg.) Infused Intravenously by Drip during the First 5½ to 7 Hours Following Exposure to Phosgene

Series	No. of Dogs	Number of Dogs Dead at:			
		24 hrs.	48 hrs.	72 hrs.	10 days
I	Infused	10	14	14	14
	Control	12	13	17	18
II	Infused	7	9	9	11
	Control	8	8	9	10
Total	Infused	17	23	23	25
	Control	20	21	26	28

The results are shown in table 2. At the end of the first series of 24 experiments, the data, although not statistically significant ($P =$ approximately 0.2), suggested that calcium-fortified Ringer's solution as administered might have some beneficial effect. However, the results of the next series of 22 experiments were negative and the totals of the two series were completely without significance ($P =$ approximately 0.6). Therefore, while this treatment was without benefit, it was also without harmful effects. This finding agreed with the better clinical appearance of the animals, as contrasted with that following plasma or gelatin infusions.

Posterior pituitary solution (Connaught Laboratories) was added to the calcium-fortified Ringer's in a concentration of 1:100, and was similarly infused in another series of 24 dogs. This combination¹³ was employed as a means of reducing pulmonary transudation by virtue of the capillary constrictor action of posterior pituitary substance.¹⁴ The mortality of the treated group was slightly, but not significantly, higher than that of the simultaneous controls. The average lung/body weight ratios in all these series were nearly identical.

Physiologic salt solution was injected subcutaneously in 15 gassed dogs, in doses of 2.5 to 15 c.c. per kg. body weight; the majority received the solution shortly after gassing. Except for a somewhat heavier lung/body weight ratio at death, the saline exerted no detectable effect.

DISCUSSION

During the first World War Underhill⁵ claimed that saline infusions when combined with venesection materially reduced the mortality of phosgene-poisoned dogs, and proposed the use of a regimen including saline infusions in field casualties. These data, however, are open to serious criticism since the control animals were not gassed concurrently with the experimental dogs. Laqueur and Magnus¹⁵ found isotonic salt solutions without

benefit in poisoned cats, while hypertonic solutions were harmful. These investigators found, as we have, that saline infusions did not prevent hemoconcentration and rarely resulted in more than transient hemodilution. In brief, evidence that saline infusions accomplish their symptomatically indicated purpose is unconvincing.

The use of infusions containing high molecular weight substances seems to warrant even more severe criticism. On the basis of clinical observation of these severely poisoned dogs, we believe that such infusions should not be employed. The difference between the effects of the two types of solutions seems the result of one or more of the following circumstances: (a) The saline was given by intravenous drip at a rate of approximately 1 c.c. per minute, while the protein solutions were given by syringe at rates 10-25 c.c. per minute; however, the similar poor results obtained by Courtice and Foss⁸ were with use of slow intravenous drip of plasma and serum. (b) The saline is a solution of low viscosity and partially reduces the viscosity of the alveolar edema; thus, although it does not cause drainage via the trachea, it probably reduces the tendency of the frothy edema fluid to form waterlocks in the bronchioles, which contribute to the anoxic anoxia. Fluids of high viscosity, on the other hand, may exaggerate the syndrome by increasing the amount of edema fluid without reducing the frothing properties. (c) While the saline solutions were infused in larger volume than was true of the high molecular weight substances, much of the saline could and probably did move into extrapulmonary reservoirs, whereas the infusions of high molecular weight were able to pass only into the lung where the capillary permeability was abnormal. Considerations such as these are implicit in the decision to use no plasma or minimal amounts in treating the shock combined with pulmonary damage in the victims of the Cocoanut Grove fire.¹⁰ Our findings support this point of view.

In regard to fluid therapy of persons with pulmonary edema from lung irritants, it appears best to give none. If it is believed necessary to control hemoconcentration and increase plasma volume, water by mouth will produce transient hemodilution nearly as promptly as parenteral fluids; if parenteral fluids are employed, we believe they should be saline solutions, not plasma or plasma substitutes. This point of view does not, of course, extend to pulmonary edema brought about by hemodynamic abnormalities in which the low protein content of the fluid indicates retention of almost normal semi-permeability on the part of the pulmonary capillaries.

In the irritant type of pulmonary edema there seems to be little chance of effectively treating the stagnant anoxia without simultaneously magnifying the anoxic anoxia. Of the two forms of anoxia, the latter is the more immediately lethal.

SUMMARY

1. A consideration of the pathologic physiology of phosgene poisoning indicates the symptomatic use of infusions, in order to control the hemoconcentration and to restore the plasma volume.

2. In phosgene-poisoned dogs concentrated plasma and pectin and gelatin solutions exerted only transient effects on the hemoconcentration, and appeared to aggravate the pulmonary edema. All of these substances appeared in the edema fluid.

3. Infusion of a saline solution by slow intravenous drip controlled hemoconcentration only during the time of administration. Ultimate survival was not improved by this infusion, although, in contrast to plasma or plasma-substitutes, it appeared to have no deleterious effects.

4. Owing to the tendency of infusions to leak out of the damaged pulmonary capillaries, the general effect of this type of therapy in phosgene poisoning is to exaggerate the already present pulmonary defect. Their use, artery. not indicated.

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CAROTID ARTERY THROMBOSIS: REPORT OF EIGHT CASES DUE TO TRAUMA *

By HAYES W. CALDWELL, M.D.,† *Phoenix, Arizona*, and FREDERICK C. HADDEN, M.D.,† *Natick, Massachusetts*

THE syndrome of a thrombosed internal carotid or common carotid artery existing for considerable periods of time without antecedent trauma has been described.⁴⁻¹¹ Acute thrombosis of the common or internal carotid artery following trauma has not been frequently reported ^{cases} clinical syndrome that is easily recognized. Errors in diagnosis ^{may occur} in the presence of small penetrating neck wounds and fractured jaws. In such instances subdural hematoma,¹⁰ cerebral vascular occlusion or hemorrhage may be mistakenly presumed to be present unless the carotid occlusion is suspected and the neck vessels dissected out at surgery or autopsy. Walker⁹ described five cases that sustained high neck or jaw wounds with contralateral spastic hemiplegia. Three of these were unconscious after wounding and the other two developed signs two and four days respectively after being wounded. In one patient the symptoms were due to an aneurysm of the internal carotid artery. In the other four, carotid thrombosis was assumed to be responsible.

The recognition of the early manifestations of carotid artery thrombosis in wounds involving the neck and mandible is important. Surgical occlusion of the vessel with a constricting band above and below the thrombus may prove to be life-saving in preventing emboli or propagation of the thrombus cephalad. Ligation of the vessel is of questionable merit as often new thrombus formation occurs at the site due to intimal trauma.¹ Anti-coagulation therapy may provide a favorable outcome to an otherwise usually fatal condition.

The material for this report was collected while treating war casualties in the European Theatre of Operations. These observations were carried out while large, at times overwhelming, numbers of casualties were being treated in a field installation and in some cases were regrettably briefly recorded. "Backlogs" of three to four hundred cases requiring surgery were not unusual. This work pressure is also reflected in the time interval between admission and surgical treatment of these reported cases. The eight cases represent .03 per cent of 25,554 admissions at the 5th Evacuation Hospital, and .08 per cent of the 8,986 cases operated upon. The number of these cases operated upon that had jaw or neck wounds in the proximity of the carotid artery is unknown. The hospital had one and sometimes two

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† Formerly Captains A.U.S., M.C., 5th Evacuation Hospital (S.M.).

designated maxillo-facial surgical teams and in some instances patients were referred specifically for this type of surgery.

All of our cases diagnosed ante mortem were observed during the last six of the 15 months that the hospital was in operation. It is most probable that other cases went unsuspected during the preceding nine months. It is unfortunate that the patients' ages were not recorded, inasmuch as it has been pointed out that carotid artery occlusion by ligature is more favorably tolerated under 40 years of age (Horsley, 1915). Most of our cases probably fell in the age group between 20 and 40 years. They presented in addition to arterial occlusion, in some cases, the problem of a thrombus propagating cephalad to involve the intracranial branches of the internal carotid artery.

CASE REPORTS

Case 1. H. S., admitted 11:30 p.m., November 30, 1944, in a semi-comatose condition four hours after being wounded by a shell fragment that entered the left side of the neck just below the jaw angle and anterior to the sterno-mastoid muscle. It travelled medialward and lacerated the left lateral wall of the pharynx. There was no active external bleeding. Blood pressure on admission 140 mm. Hg systolic and 60 mm. diastolic, pulse 38. At 7:00 a.m., December 1, 1944, the laceration in the pharynx was sutured and the neck wound debrided and closed with drainage. Sulfadiazine was placed in the wound and 20,000 units of penicillin were given subcutaneously every three hours. Gas, oxygen, and ether served as anesthesia. The patient failed to respond after the operation and became comatose. Cyanosis developed and many coarse râles were heard throughout both lungs. The neck, shoulders and trunk became edematous and the skin light brick-red in color. The color blanched temporarily on pressure. The edema was non-pitting. Obstruction of the airway was suspected and the patient returned to the operating room where a bronchoscopic examination was made, at which time a large amount of blood and mucous material was aspirated. A tracheotomy was performed while the patient was in the operating room. The patient was returned to the shock ward with blood pressure 128/65, pulse 92. The following day, December 2, at 12:15 a.m., he appeared to improve and became restless, but never regained consciousness. Pupils were equal and reacted actively to light. The head diverted and rotated to the right and was returned to this position when moved. The deep reflexes were hyperactive bilaterally, but more exaggerated on the right. There was bilateral ankle clonus. The Babinski sign on the right was 4 plus and 2 plus on the left. Blood pressure 160/75, pulse 88, temperature 102° axillary at 2:00 a.m. Spinal puncture revealed clear fluid under increased pressure. Bilateral temporal pulsations were noted. Thrombosis of internal carotid on the left was diagnosed. The patient became cyanotic and respirations ceased entirely at 3:30 a.m., December 2, but were started again after artificial respiration and intravenous injection of coramine and adrenalin. By means of a catheter attached to a suction pump, large amounts of mucoid blood-tinged secretions were removed through the tracheotomy opening. One-half hour later his respirations stopped again and failed to start after artificial respiration was carried out for one and one-half hours, although during this time his pulse remained full and regular.

Autopsy examination revealed the wound tract that extended into the pharynx just above the larynx. There was no evidence of laryngeal obstruction. Dissection of the neck vessels disclosed a small 1 cm. laceration of the adventitia of the left internal carotid artery extending only to the media. This laceration was filled with

blood clots. The internal carotid was filled with an organized thrombus that extended toward the heart to the bifurcation of the common carotid and toward the brain including the vessels making up the left half of the circle of Willis. The brain was described as softer on the left than on the right. Microscopic examination confirmed the presence of antemortem thrombosis in the internal carotid artery and the circle of Willis. Hemorrhage was present in the adventitia of the internal carotid but it was otherwise normal. Sections of the left cerebral hemisphere revealed marked vascular congestion with numerous small focal hemorrhages. The basic fibrillar network of the tissue appeared rarefied and there was some anatomical disruption. The neurones were not necrotic and showed only chromatolytic changes. Sections of the right cerebral hemisphere were normal.

This was the longest time we supported any patient in this series with artificial respiration. We realized it was a futile gesture, but wished to establish the fact that respiratory failure occurred some time before the heart stopped beating. The respiratory failure was no doubt of central origin.

Case 2. T. F., admitted 9:00 p.m., February 6, 1945, with gunshot wound of entrance in the left cheek opposite the first molar tooth. The bullet travelled posteriorly and downward to its point of exit, posterior to the sternomastoid muscle in the mid-neck region. There was also a laceration of the left shoulder, probably due to the same bullet in its exit. There was no active bleeding from the wounds but the neck was swollen. The airway was judged to be adequate. Blood pressure 110/80, pulse 92. Patient was stuporous and unable to talk, but he would open his eyes and was able to look both to the right and to the left. There was no demonstrable facial paralysis, but both arms were paralyzed, the left flaccid and the right spastic. Both legs were moved actively upon stimulation. The knee jerks and ankle jerks were equal and hyperactive. There was a sustained ankle clonus on the right. Bilateral normal plantar response to stimulation. The abdominal and cremasteric reflexes were absent bilaterally. The temporal pulse was absent on the left but normal on the right. Thrombosis of the left common carotid artery was diagnosed.

At 2:00 a.m., February 7, 1945, the face and neck wounds were debrided. In the absence of active bleeding the carotid artery was not explored. At the end of the operation the blood pressure was 125/80, pulse 112, temperature 100.6, respirations 20. Reexamination February 8 revealed a facial paralysis on the right. The patient was incontinent and restless, actively moving both legs. There was a flaccid type of paralysis of the right arm. Painful stimulation elicited a shrugging elevation movement of the left shoulder girdle. The eyes appeared normal except that the left pupil was constricted while the right appeared normal in size and reacted to light. During the day 3,000 c.c. of 5 per cent glucose were given intravenously. February 9, 1945, it was noted that the patient's course was progressively downward and he appeared less responsive. He was able to move only the left leg and it was observed that his head would rotate and fall to the right. The pupils had become equal and normal in size. Both arms were flaccid. The knee jerks were active on the left but absent on the right. The Babinski sign on the right was positive and negative on the left. There was a bilateral unsustained ankle clonus. Lumbar puncture was done and revealed clear fluid with initial pressure 320 mm. of water, and after 30 c.c. were removed, the pressure fell to 150 mm. of water. There was definite but brief improvement after the spinal puncture but the patient's course later continued to deteriorate and he died February 10 at 5:30 a.m. Other treatment consisted of 20,000 units of penicillin given every three hours subcutaneously and sulfadiazine intravenously.

Autopsy: The neck was dissected out and examination of the carotid artery revealed lacerated wounds of both the left internal and external carotid arteries near the bifurcation of the common carotid. Both vessels were filled with antemortem thrombus that extended up into the neck as far as the dissection could be carried in the neck and downward to occlude the common carotid. The intracranial portion of the internal carotid was filled with a thrombus that extended into the left middle and anterior cerebral arteries. The right half of the circle of Willis and the major branches were patent. The left cerebral hemisphere appeared soft and on section multiple gross "petechial hemorrhages" were observed. Microscopic examination of a section of the left cerebrum was reported as follows: "The vessels tend to be congested. Many small focal hemorrhages are present. The neurones show changes varying from chromatolysis to necrosis. The brain tissues show mechanical disruption of the architecture and are infiltrated by many polymorphonuclear, lymphocytic and phagocytic cells. Some of the latter are grouped about degenerative and necrotic neurons. Many polymorphonuclear cells are seen in the perivascular spaces." Microscopic examination confirmed the presence of an antemortem thrombus occluding the left cerebral and left carotid arteries.

Case 3. E. G., admitted 7:00 p.m., April 17, 1945, in deep coma. His field records indicated that he had received a "gunshot wound" at 3:00 a.m., April 17 that produced a severe laceration of the left neck extending from the midline anteriorly to the tip of the mastoid bone posteriorly. All structures were involved down to the great vessels. There was also a compound comminuted fracture of the left mandibular ramus and a "penetrating wound in the left neck." A tracheotomy tube was in place. Examination revealed only a slight amount of blood stain on the dressings. Further examination revealed the left temporal pulse to be absent, the right normal. The right pupil was normal in size and reacted promptly to light; the left was dilated and failed to react to light. Ophthalmoscopic examination revealed the left disc to be obscured by edema. The retinal arteries were thread-like and pale, the veins appeared tortuous and pulsated. The right fundus appeared normal. The right arm and the right leg were paralyzed but the right shoulder girdle moved in an elevated shrugging fashion upon painful stimulation. The abdominal and cremasteric reflexes were absent bilaterally. There was a bilateral unsustained ankle clonus. The right Babinski reaction was positive. The plantar response on the left was normal. Blood pressure 112/94, pulse 116, respirations 28 per minute.

Thrombosis of the left common carotid with extension of the thrombus into the internal carotid artery and involving the ophthalmic artery and the circle of Willis was diagnosed. The surgeon was asked to examine the common carotid artery in his exploration of the wound.

On April 18, at 3:00 a.m., under ether anesthesia the fractured mandible was reduced and wired. The neck wound was explored and the carotid artery exposed; there was no noticeable trauma to the vessel and it appeared to pulsate normally. The surgeon felt that the vessel was not thrombosed. After surgery, the patient's condition deteriorated and he died 12:20 p.m. April 18, 1945. The use of heparin was considered but the patient died before it could be started. Autopsy revealed thrombosis of the left common carotid artery that extended toward the brain and occluded the external carotid, internal carotid, left ophthalmic and the left middle cerebral arteries. Externally the common carotid appeared grossly normal. When this vessel was opened longitudinally, a transverse tear through the intima down to the media was found which extended over about one-fifth of the circumference of the vessel. The thrombus was firmly attached here and had propagated from this site cephalad (figure 1). The left cerebral hemisphere was described as being soft by the pathologist.

Microscopic examination: "There is an antemortem thrombus filling the lumen of the common carotid artery. Inflammatory cells, polymorphonuclear and lympho-

cytic cells have infiltrated into the media and adventitia. There is hemorrhage into the adventitia." Sections of the left cerebral hemisphere revealed the "subpial blood vessels are congested," otherwise the brain substance was reported as normal.

Case 4. J. J., age 20, admitted 9:00 p.m., January 19, 1945, the day of the injury, which occurred when his truck overturned on an ice-covered highway. Apparently he was momentarily "stunned" and following this he had a lucid interval that lasted for four hours after the injury. Examination upon admission disclosed a semi-comatose patient with (1) compound comminuted fracture of the right mandible near the angle, (2) simple fracture of the left clavicle, (3) superficial laceration of the anterior triangle in the right neck. The jaw fracture was reduced 2:00 a.m. January

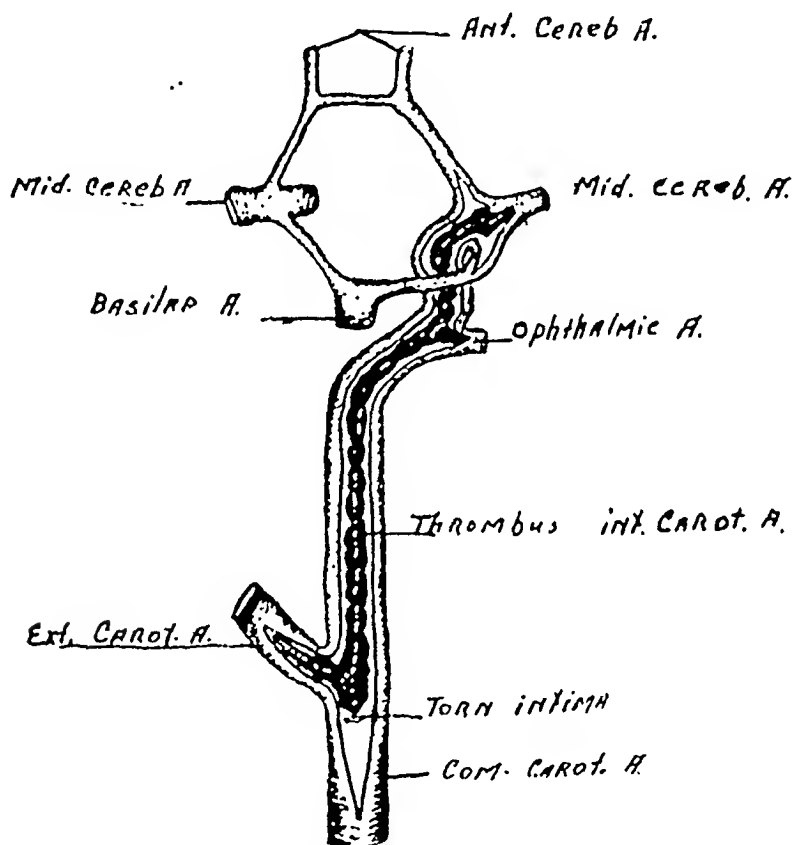


FIG. 1. *Case 3.* Thrombus originating in the common carotid artery and extending cephalad.

20, 1945. Skull roentgen-rays made at this time were negative for fractures. Blood pressure 130/92, pulse 124, respirations 26. After surgery he vomited several times and became incontinent; the coma deepened. There was extensive ecchymosis involving the eyelids bilaterally and the right mastoid areas. The left eyelid was ptosed and there was twitching in the left facial muscles. The pupils were small, equal, and reacted actively to light. The left arm and leg were paralyzed. The left cremasteric reflex was absent but normal on the right. The knee jerks were bilaterally hyperactive and the Babinski sign positive bilaterally. There was no ankle clonus.

In view of the history of a lucid interval occurring after the head injury, it was imperative to rule out the probability of subdural hematoma. Under local anesthesia, 3:00 p.m., January 20, bilateral temporal and parietal burr holes were made. The dura was normal and the cortex appeared normal. Attempted ventricular puncture on the right side was unsuccessful. Left ventricular puncture yielded 4 c.c. of clear

colorless fluid. After surgery the patient was able to respond with "uh huh" several times on stimulation. Pulmonary edema then developed and he rapidly failed. At 7:00 a.m. January 21, the patient suddenly stopped breathing and died.

Autopsy revealed thrombosis of the right common and external and internal carotid arteries. The artery, when opened, revealed a most unusual picture. The intima had been torn completely through in a circumferential direction. The cephalic section had then been peeled off the media and the free edge curled upward extending into the external and internal carotid arteries and giving the appearance of valves in these vessels (figure 2). The vessels were filled with thrombi. The intracranial part

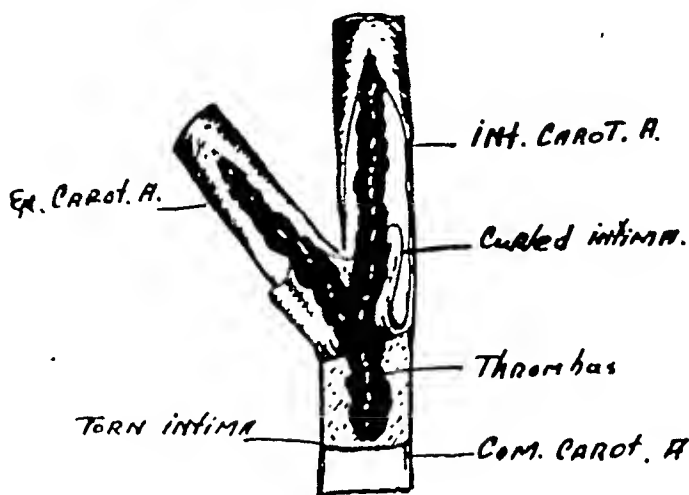


FIG. 2. Case 4. Intima of the common carotid artery torn and stripped off the media. The free edge was curled upward to form false valves for the internal and external carotid artery. Thrombus extending into these vessels from its origin in the common carotid artery.

of the internal carotid and its branches were grossly normal and the circle of Willis appeared normal. Examination of the brain revealed the right hemisphere to be soft and on section many petechial hemorrhages. The microscopic sections of the carotid artery revealed "fragmentations of the vessel wall with areas of hemorrhage, and infiltration by many polymorphonuclear cells." The lumen was filled with an ante-mortem thrombus. Sections of the brain revealed "congestion of the veins but no other changes are recognized."

Northcroft and Morgan¹⁰ described in their case a similar picture of false valve formation following the transverse tearing through of the common carotid intima with further separation of the distal part to form such a false valve. In their case the injury occurred when a dangling rope on a passing truck wrapped around a soldier's neck and threw him down.

Case 5. K. S., German prisoner of war, was admitted 2:00 p.m., April 8, 1945 with: (1) Gunshot wound of the anterior neck at the level of the thyroid cartilage with the wound of exit $1\frac{1}{2}$ " below the left ear; (2) perforating gunshot wound of the left arm with compound comminuted fracture of the humerus. The time and date the injuries had occurred were unknown. The patient was conscious and coöperative but dyspneic and cyanotic. Obstruction to the airway was suspected and bronchoscopic examination and afterwards a tracheotomy were carried out. The wounds were debrided. On the fourth post-operative day he became irrational. The cyanosis and

dyspnea reappeared and he died 7:00 p.m., April 12, 1945. No notes of a neurological examination were made on the chart.

Autopsy revealed bilateral pulmonary edema of the lower lobes. Dissection of the neck vessels revealed a thrombosis of the left internal carotid artery. The autopsy protocol fails to show whether the brain was examined. Likewise there is no report of the microscopic examination of the artery.

Case 6. F. K., German prisoner of war, admitted 4:30 a.m., December 23, 1944, with: (1) Compound fracture, mandible, symphysis with loss of bone; (2) compound fracture of the hyoid bone. Information as to the cause and time of his injury was not obtainable. Because of respiratory distress, the patient was immediately taken to the operating room where a tracheotomy was carried out. He was given, at the time, 500 c.c. of whole blood after which his blood pressure ranged from 160/80 to 124/70, pulse 128, respirations 24. On December 25, at 6:50 a.m., his wounds were debrided and the mandible fracture reduced. After surgery he became cyanotic and his respirations were quite shallow. Oxygen and coramine were given with a temporarily favorable response. After operation, for the first time, it was noted that the patient had a right facial paralysis and flaccid paralysis of the right arm and leg. The knee jerks were hyperactive bilaterally. The pupils were constricted and failed to respond to light. The ocular fundi were normal. Spinal puncture revealed clear fluid under normal pressure. The patient's course was progressively downward, pulmonary edema developed and he died at 10:00 p.m., December 25, 1944. Autopsy revealed extensive pulmonary edema involving the lower lobes. The left cerebral hemisphere was mildly edematous and on sectioning there were many scattered punctate hemorrhages. The right hemisphere was normal. The vessels of the brain were examined and found to be normal.

Unfortunately the pathologist was not asked to dissect out the neck vessels in this case. The attending medical officer did not suspect a carotid artery thrombosis, but suspected a thrombosis of the right middle cerebral artery. We include this case only as one suspected of having an occlusion of the left internal or common carotid artery.

Case 7. R. C., admitted 7:30 p.m., November 4, 1944 with a compound comminuted fracture of left mandible due to a shell fragment which remained in his left neck. The wound of entrance was 1 in. below and anterior to the left ear. It was received at 11:15 a.m., November 4, 1944. At 4:30 p.m., November 4, 1944, at another hospital, he was thought to have an intracranial injury because he became "irrational and the pupils were unequal." Roentgen-ray examination revealed a huge foreign body at the level of C-4 on the left. He was in deep coma and occasionally grunting. Eyes tended to rotate upward and the left pupil was slightly dilated. Both pupils reacted actively to light. There was flaccid paralysis of all four extremities except the left leg which was moved upon stimulation. The abdominal and cremasteric reflexes were absent. The patellar reflexes were active. The Babinski signs were absent and there was no ankle clonus. The patient was voiding and defecating involuntarily. Blood pressure 102/71, pulse 92, respirations 29. After two blood transfusions (1,000 c.c.) the blood pressure went up to 130/76; pulse 96, respirations 24. The patient was thought to have a large hematoma pressing on and occluding the left carotid artery. He was taken to surgery at 3:30 a.m., November 5, 1944, and with 1 per cent Novocaine locally injected, the wound was explored. The foreign body measuring 1" by $\frac{3}{4}$ " by $\frac{1}{2}$ " was found to be lying on the common carotid artery sheath just below the angle of the mandible. There was a moderate hematoma in the neck adjacent to the carotid artery. The metal fragment was removed without trauma to the carotid artery which was described as being normal to inspection. The mandible

fracture was reduced and wired in place. Blood pressure after surgery (6:15 a.m.) was 122/74, pulse 100. Three hours after surgery his respirations failed despite injections of coramine and administration of artificial respiration. The pulse was observed to remain regular and full even after respirations had ceased. He died at 4:45 a.m., November 5, 1944.

Autopsy examination: There was bilateral pulmonary edema of all lobes of the lungs. The brain was described as follows: "When the dura was opened the convolutions were found to be flattened. There were hemorrhages (punctate) into the brain on the left side." The neck vessels were unfortunately not dissected out and there were no microscopic sections made of the brain.

This was one of the earliest cases we observed and in view of our later experience we feel sure that the left carotid artery was thrombosed.

The final case was diagnosed as thrombosis of the internal carotid artery. We debated whether to attempt ligation of the internal carotid artery or to use heparin. In view of our previous autopsy findings it was decided that the surgical attempt might require the exposure of the entire internal carotid in the neck to get above a propagating thrombus, or the exposure of this vessel in the cavernous sinus; and would be technically too difficult. Inasmuch as the surgical repair of his wounds had occurred three days before symptoms appeared, treatment with heparin was elected.

Case 8. J. M., admitted 3:00 p.m., April 9, 1945 with a gunshot wound that occurred 9:00 a.m., April 9, 1945. The bullet entered the left cheek at the level of the posterior molar tooth, passed through the mouth and lodged in the right side of the neck near the jaw angle. The patient gave a history of having been knocked unconscious when he was wounded. After recovering consciousness he was able to walk about a mile to the aid station. He vomited repeatedly en route. On admission to our hospital he was conscious and able to move his arms and legs. On April 9, the face wound was debrided and the bullet in the right neck at the jaw angle was removed. On April 13, the nurse noticed he was semi-stuporous, and could be awakened only with active stimulation. The patient complained of severe frontal headache. Examination revealed that the temporal artery pulsations were present bilaterally. The left eye deviated toward the midline and diplopia was experienced upon looking to the left. Pupils were normal in size, round, equal and reacted to light. Ophthalmoscopic examination was reported as normal. There was a central type of facial paralysis on the left and a flaccid paralysis of the left arm and leg with associated absence of the left abdominal reflexes. The knee jerks and ankle jerks were equal and normally active. There was a positive Babinski sign on the left, no ankle clonus. A diagnosis of thrombosis of the right internal carotid artery was made.

Heparin* was started April 12, 1945 (100 mg. in 3,000 c.c. of normal saline, were given in divided doses over a 24 hour period). Coagulation times (capillary method) was checked every eight hours. He was given the same dosage of heparin for the next 64 hours. The clotting time varied between 12 and 35 minutes during the time he received the drug.

The day after institution of heparin therapy there was no essential change to be detected upon neurological examination. On April 14 (second day of treatment) the patient was alert enough to smoke a cigaret. He was able to rotate his eyes to the left of the midline, and could voluntarily move his left leg a small amount. At this time he had a sustained ankle clonus on the left. On April 15 the strabismus had disappeared. The ophthalmoscopic examination appeared normal except for a marked

*Lt. Col. Robert Stoner kindly supplied the heparin.

spasm of the arteries in the right fundus. On April 16 he was able to move the left leg freely but unable to move the left arm. He complained of tingling sensation in the left arm. The facial paralysis appeared less pronounced, although the frontal headache was still severe. The strabismus had completely cleared. On April 17 the sutures were removed from his wounds and a moderate amount of liquid sanguineous fluid was allowed to escape. The patient was evacuated to a rear medical installation on April 18. Communication received from the patient dated April 29, 1945 stated: "I am getting better every day. My leg has come back to life and I am getting a little use out of my arm."

DISCUSSION

Injury to the common carotid artery may cause: (1) Profuse hemorrhage and death; (2) extravasation of blood into the surrounding tissue forming a hematoma that may occlude the vessel due to pressure (Schwarzald); (3) the development of a false aneurysm as a later sequela²; (4) the development of an intravascular thrombosis which (a) early, before the vessel is occluded, may serve as a source of emboli to branches of the internal carotid artery, or (b) after the vessel is occluded it may propagate in either direction. The cephalad propagation may occlude the external carotid and the branches of the internal carotid including half of the Circle of Willis with resulting infarction of the involved cerebral hemisphere. There is a common supposition by some that arterial thrombi do not propagate beyond a major vessel branch. As pointed out by Dandy this theory was apparently first proposed by Jones (1802). However, this idea was refuted by Travers (1813) who stated "that the thrombus is not bounded by collateral branches, but extends into them."¹ This statement is borne out by the findings in our cases. It is the prevention of this propagation of the thrombus that is most important in the treatment of these cases.

Handley and Oldfield have pointed out that hemiplegia resulting from carotid artery occlusion may occur as a result of (1) inadequate collateral circulation through the Circle of Willis; (2) thrombosis spreading to occlude the Circle of Willis; (3) embolism to the cerebral vessels. The cases we are reporting demonstrate in one instance the occlusion of half the Circle of Willis. Two cases had occlusion of major cerebral vessels, and in two cases the thrombus apparently was confined to the internal carotid artery.

Surgical occlusion of the vessel and possible resection above and below the thrombus is possible if carried out early. The distal occlusion of the vessel may be best carried out through an intracranial approach. Because of technical difficulties this procedure would be best carried out only by an able neurosurgeon. Metal bands would appear to offer the best means of ligation.¹ The accepted procedure is to first test the collateral circulation by doing the Matas test (digital pressure on the internal carotid for 10 minutes).¹ However, ligation of the common, external, and internal carotid has been carried out without preliminary compression.

Anticoagulants in selected cases would appear to be worth while. Luke and Winter have reported successfully using heparin in the treatment of

carotid artery thrombosis and we used it also with good results in one case. There is the danger of bleeding from the site of injury in the neck, but this, despite the hazards of local hemorrhage, is worth a trial. The amount of anticoagulant should be controlled with frequent determinations of the prothrombin time as suggested by Allen and others.¹² The thrombosis, in our experience, spreads rapidly and had often impaired the cerebral circulation before the true nature of the lesion was recognized.

The absence of the temporal pulse on the involved side is good confirmatory evidence that the common carotid and possibly the external carotid is occluded. This sign is of value also in indicating to the surgeon the extent to which the carotid vessel must be dissected if surgery is the elected type of therapy. The absence of the right radial pulse may indicate that the subclavian artery is also occluded by the thrombus propagating toward the heart.⁴ One cannot help but surmise from a review of the literature that thrombosis of the carotid artery occurs more frequently than is reported. It is suggested that exploration of the carotid vessels at autopsy by dissecting or probing would demonstrate the true etiology of some cases of "apoplexy" that the pathologist otherwise finds difficult to demonstrate on examination of the cerebral vessel.

SUMMARY

1. Eight cases of post-traumatic carotid artery thrombosis have been presented.
2. Five cases were proved at autopsy to have a thrombosis of the common and/or internal carotid artery.
3. Two cases were presented in which the diagnosis was not suspected prior to death and not investigated at autopsy.
4. Recovery in one case was apparently due to heparin therapy.
5. The authors feel that acute carotid artery thrombosis may occur more frequently than the reported cases in the literature would indicate.

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MASSIVE DOSAGE OF PENICILLIN ADMINISTERED BY CONTINUOUS INTRAMUSCULAR INFUSION *

By RALPH LEE FISHER, A.B., M.D., F.A.C.P., and MORRIS ZUKERMAN,
A.B., M.D., *Detroit, Michigan*

WE wish to present a review of our experience with 24 patients treated with a massive dosage of penicillin by continuous intramuscular infusion.

The dose varied from 500,000 to 2,000,000 units of penicillin administered daily for a period of three to 19 days. The first nine patients were given crude penicillin and the last 15 penicillin G.

Technic of Administration: The penicillin was dissolved in 500 c.c. of 5 per cent glucose in water. A No. 20 gauge spinal needle was inserted in the lateral aspect of the thigh after infiltration with 1 per cent procaine hydrochloride. Ten c.c. of 1 per cent procaine hydrochloride were added to the penicillin solution and slow, continuous infusion was started. Five hundred c.c. of the solution were administered each 24 hours which necessitated that it run at an average of four to six drops per minute. It was found advantageous to insert the needle into the opposite thigh every three to four days. It was necessary to discard the spinal needle after an average of two to three courses of penicillin since the needle became rusty and broke easily.

Indications: This technic of administering penicillin was employed under the following circumstances: (1) when a massive dosage was indicated; (2) when nursing staffs were busy and undermanned; (3) when hospitalization was not feasible; (4) when the patient objected to multiple injections; (5) and when veins were not available for intravenous therapy.

Value of the Technic: The administration of penicillin by this technic was indicated when a large dosage was required. By administering penicillin in this manner, one was able to reduce the work of the nursing staff. Once the needle was in place, the only work required of the nursing staff was that of attaching a new flask of solution at the end of 24 hours. We have found that after the patients are instructed how to regulate the rate of flow, the nurses are relieved of the burden of continuously checking the solution.

In cases where hospitalization was not feasible, we have found it practicable to treat such patients in the home. After placing the needle in the thigh and starting the initial flask of solution, the patients' relatives were instructed as to the rate of flow and how to change the flask. From then on, the relatives of the patients were told to come to the clinic and obtain the solution. They were also advised to notify us of any unusual reactions or complications and were informed how to discontinue therapy. One or two home visits during the course of treatment were made to check the progress of therapy.

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From the Department of Medicine, Riverside Clinic, Detroit, Michigan.

This technic has proved valuable also for those patients who objected to multiple injections. The patients are able to enjoy bathroom privileges since they may be ambulatory, if the leg and thigh are not flexed unduly, without danger of breaking the needle. It has been possible to administer large doses of this drug when no veins were available. This method has given higher blood levels over a 24 hour period than any other technic of administration of penicillin available. Hirsch and Dowling¹ observed that the administration of penicillin by a series of single injections would not maintain blood levels as high as when the drug was given by continuous intramuscular drip. They noted that with injections of 25,000 units every three hours or 20,000 units every two hours, the blood penicillin concentrations one hour after each injection were not as high as were the levels when using continuous intramuscular infusion of a total of 200,000 units within a 24 hour period. Two to three hours after a single injection penicillin was often undetectable in the blood. These authors found a concentration of 0.039 unit of penicillin per cubic centimeter to be efficacious against most penicillin susceptible organisms. Using this level as a criterion, three patients were given 25,000 units of penicillin by intramuscular injection every three hours. An adequate concentration of penicillin was present, in 16 or 80 per cent of 20 determinations. In nine patients given 20,000 units every two hours, a level of 0.039 unit per cubic centimeter or above was found in 51 (67 per cent) of 76 determinations. Following the administration of 15,000 units every two hours, this same level was obtained in only 29 (63 per cent) of 46 determinations. Twenty-five patients received 200,000 units of penicillin by continuous intramuscular infusion. When the blood was examined at intervals during the 24 hour period, therapeutically effective blood levels were discovered in 142 (96 per cent) of 152 determinations. The same authors showed that when 8333 units of penicillin were given per hour by continuous intramuscular drip, 96 per cent of the blood penicillin concentrations were therapeutically effective. McAdam² showed that six times as much penicillin was required to maintain a bactericidal level when the drug was given at intervals of four hours as when it was administered by continuous intramuscular drip; three times as much penicillin was required when the interval was three hours and at least one and one-quarter times as much when the interval was two hours. Hirsch and Dowling¹ noted that by use of the continuous intramuscular method blood concentrations of penicillin similar to those observed during continuous intravenous injection could be obtained with 50 per cent less penicillin.

Early in this series the technic of determining penicillin levels had not been developed. In two of our later cases who received two million units daily, the level ran 0.5 and 4 units per cubic centimeter of blood serum respectively.

Reactions: The reactions following continuous intramuscular penicillin consisted of two types: local and systemic. Local reactions consisted of the following:

(1) Cellulitis of the thigh. Redness of the thigh appeared on an average of 3.75 days after therapy was initiated. The inflammation was noted after an interval averaging seven days when crude penicillin was used and 2.26 days when penicillin G was administered.

(2) Pain in the thigh. The pain consisted of two types: that noted at the time on firm palpation of the thigh, and that noted after therapy was discontinued. Pain on palpation appeared on an average of 2.79 days following the introduction of this therapy. When crude penicillin was used, this reaction was noted on an average of four days after therapy was started and for penicillin G on an average of 2.06 days. Pain which was noted after therapy was discontinued, lasted from seven to 10 days. An occasional patient who received his penicillin rapidly developed instant pain at the site of injection. This was corrected by reducing the rate of flow.

Smith and Harford³ reported 10 patients who developed severe inflammatory reactions at the site of injection. In nine patients the reaction developed on the fifth to seventh day of treatment and consisted of severe local pain, redness, and heat about the site of injection, the whole lateral aspect of the thigh being involved as a rule. The inflammatory process subsided rapidly, usually within 24 hours after the needle was removed. They believed that the reactions were the results of the impurities in the penicillin.

(3) Abscess formation at the site of injection. Abscesses were of two types, the ones noted immediately during treatment and the delayed type which came to our attention after treatment had been discontinued. Four patients developed abscesses; two of these were of the delayed type and followed the use of crude penicillin. One abscess came to our attention 19 days after therapy began and a second 90 days after therapy was started. The abscesses that resulted while using crude penicillin were larger than those following penicillin G. The delayed form was important because of the possible medico-legal aspects.

Jones and Williams⁴ have reported the case of a patient who developed aseptic necrosis at the site of continuous intramuscular penicillin infusion. Morgan, Christie, and Roxburgh⁵ have reported two patients who developed local abscesses around the site of the needle puncture following systemic administration of penicillin. Cultures of the pus produced a growth of coliform bacilli. In one of the cases, the blood level fell until it was hardly detectable, presumably since no penicillin was absorbed from the abscess cavity. The abscesses in both cases were opened and healed in three weeks. The delayed abscesses in our patients revealed approximately 200 c.c. of a chocolate colored fluid which did not have an odor. The immediate abscesses contained approximately 50 to 100 c.c. of sero-sanguineous fluid and culture did not result in a bacterial growth. The abscesses were usually treated by making a small incision over the area of fluctuation. Healing took place in three weeks.

(4) Subcutaneous emphysema. This condition was noted in one patient five days after therapy was started and lasted for a total of nine days. This

reaction must have resulted from the failure to remove all the air from the tubing prior to initiation of therapy. Smith and Harford³ described intramuscular and subcutaneous emphysema in one of their patients when the drip was allowed to run out. The reaction subsided promptly.

(5) Phlebothrombosis. Smith and Harford³ reported phlebothrombosis of the femoral vein in one of their patients which was probably a result of inflammation of the tissues around the vein. The needle had been inserted into the anterior aspect of the thigh. This reaction did not occur in our patients.

Systemic Reactions: (1) Elevation of temperature. This was the second most common reaction noted. It was possible to draw deductions as to febrile reactions to the treatment in 16 patients. The remainder of the patients had an elevated temperature at the time the treatment was initiated, and any pyrexia produced by the penicillin could not be evaluated accurately. In the group of 16 patients the highest temperature noted during the administration of penicillin was 103.4° F., which appeared four days after therapy was started. The average temperature of the 16 patients during therapy was 101.5° F. Seven patients who were given crude penicillin had an average elevation of temperature of 2.1 degrees while those patients receiving penicillin G had an elevation of 3.8 degrees. An interval of 7.7 days elapsed before pyrexia was noted in those patients receiving crude penicillin and 3.7 days in those patients given penicillin G. The temperature returned to normal on an average of 12 to 17 hours after the needle was removed from the thigh. Smith and Harford³ recorded pyrexia as the second commonest reaction in their patients. An elevation of temperature occurred on the sixth or seventh day and returned to normal within 24 hours after therapy was discontinued. All their patients who developed fever showed evidence of local inflammatory reaction at the site of injection although the reverse was not true; this latter point was in keeping with our observation.

(2) Allergic manifestations consisted of urticaria and delayed serum sickness-like reaction. One patient developed delayed serum sickness-like reaction to crude penicillin. The reaction began the first day after therapy was discontinued and reached its peak on the third day. Two patients developed urticaria which appeared 11 and 14 days respectively following the initiation of treatment. One patient had received crude penicillin and the second penicillin G. It should be stressed that the mode of administration and the dose of penicillin do not influence the production of these allergic manifestations. Keefer⁶ found urticarial reactions in 14 or 2.8 per cent of 500 patients who received penicillin. Moore⁷ treated 1418 syphilitic patients with penicillin and eight patients or 0.56 per cent developed urticaria. The general conclusion was that urticarial reactions are not frequent, and that delayed serum sickness type of reaction is even more uncommon, possibly one in 1500 or 2000 cases. Gordon⁸ reported three cases of delayed serum sickness-like

reaction to penicillin which developed two to seven days following cessation of penicillin treatment. Baker and Lyons⁹ stated that urticarial and delayed serum sickness-like reactions which followed penicillin therapy, were the result of impurities in the preparation. The preponderance of opinion and laboratory studies pointed to the fact that there was an anaphylactic sensitization by the penicillin itself in a susceptible individual with resultant true allergic manifestations, such as are found with sensitization to true proteins.⁶ For the urticarial and delayed serum sickness-like reactions, calamine lotion was applied to the skin and benadryl 50 mg. after meals and at bedtime was given. This controlled the pruritus effectively.

(3) Leukocytosis. It was possible to check the leukocyte count in only four patients; the average count was 13,800. Smith and Harford⁷ noted that their patients developed fever and leukocytosis of 15 to 18,000 without significant shift in the differential count.

(4) Chills. Four patients developed chills, one having been treated with crude penicillin and three with penicillin G. The chills appeared on an average of four days after therapy was started and lasted from 30 to 60 minutes. In one patient the penicillin solution was accidentally permitted to run in rapidly and a chill resulted instantly. The other patients developed their chill while receiving penicillin slowly.

(5) Anorexia. The onset of anorexia was determined accurately in only five patients and appeared 11 days after therapy was initiated. The causes for anorexia were chills, fever, inactivity, and pain.

(6) Weight loss. This was noticed in all patients and was probably due to a combination of their illness, tenderness at the site of injection, fever, and/or chills.

(7) Herxheimer reaction. Tucker and Robinson¹⁰ described probable Herxheimer reactions following the treatment of neurosyphilitic patients with penicillin. The febrile response associated with penicillin administered for syphilis has been generally accepted as the usual Herxheimer phenomenon. One patient who was treated for a gumma of the soft palate developed a severe chill instantly and a fever of 103° F. within a half hour after penicillin had been permitted to run into his thigh, at a rapid rate. The elevated temperature persisted for six days after the penicillin was reduced to four to six drops per minute. Twelve hours after the needle was removed from his thigh the temperature returned to normal.

Complications: The following complications were noted: (1) Broken needles. There were two patients who suffered broken needles at the time of receiving therapy. Both were removed easily under local anesthesia. This complication resulted when the spinal needles were used repeatedly and were weakened at the hub where they broke. We have not noticed this complication since all spinal needles have been discarded if they show any evidence of unusual discoloration or bend easily. (2) Plugged needles. This is not a common complication but when it occurred, sterile saline solution

was injected under pressure. This usually opened the needle and permitted therapy to continue. It was uncommon for a needle to become plugged so that no fluid could be forced through it. In the latter instance, a new needle was inserted either into the same or the opposite thigh. (3) Leakage around the site of the needle puncture. This was an infrequent complication which was not troublesome inasmuch as the amount of solution lost was small. A bath towel was placed beneath the thigh to absorb the fluid which escaped.

SUMMARY AND CONCLUSIONS

Observations based on experience with 24 patients treated with a massive dosage of penicillin by continuous intramuscular drip have been presented. The first nine patients were given crude penicillin and the last 15 penicillin G. The drug was administered for a period of three to 19 days. The technic of administration has been discussed. The indications for this type of treatment are: (1) where massive doses are indicated; (2) when nursing staffs are very busy and undermanned; (3) when hospitalization is not feasible; (4) when the patients object to multiple injections; and (5) when veins are not available for intravenous therapy. This method of administration of penicillin is effective as demonstrated by the fact that our patients made excellent recoveries and included in this group were seriously ill patients with subacute bacterial endocarditis, septicemia, bilateral lobar pneumonia, and lung abscess. It has been demonstrated conclusively by others that the blood levels following this method of injection are higher and fluctuate less than when penicillin is administered by any other route.

The reactions noted were local and systemic. Local reactions consisted of cellulitis, pain and abscess formation of the thigh, and subcutaneous emphysema. Phlebothrombosis of the femoral vein did not occur in our series but has been reported elsewhere. The systemic reactions consisted of elevated temperature, allergic manifestations (urticaria and delayed serum sickness-like reaction), leukocytosis, chills, weight loss, anorexia, and Herxheimer phenomenon. Complications of this therapy consisted of broken and plugged needles and leakage around the point of entrance of the needle into the thigh. The treatment of these complications has been described.

In spite of the reactions and complications noted in this form of therapy, we feel that this technic of penicillin administration is definitely indicated under the conditions described above and possesses advantages where a massive dosage of penicillin is required. With the progression of time, many organisms have become penicillin resistant to small doses, and it is necessary to use massive doses to achieve a therapeutic effect. Those who have used this form of therapy have felt that a pure form of penicillin might avoid reactions. The last 15 patients presented all of the reactions noted with crude penicillin and it was, therefore, our feeling that these reactions could not be avoided regardless of the type of penicillin used.

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THE TREATMENT OF ANGINA PECTORIS WITH PROPYLTHIOURACIL *

By GEORGE HOLLANDER, M.D., *Philadelphia, Pennsylvania*, and HARRY
MANDELBAUM, M.D., F.A.C.P., *Brooklyn, N. Y.*

EFFECTIVE and striking results in the treatment of angina pectoris have been obtained with total thyroidectomy.^{1,2} Its shortcomings—the risk of surgery, subsequent complications and irreparable loss of thyroid function—have limited its use to patients with a fair life expectancy who are adequate surgical risks. At the present time, drugs which selectively act to block the formation of active thyroid hormone to give rise to a reversible, chemical thyroidectomy, include radioactive iodine and the thiouracil group. In many, these are a medical substitute for surgery, without its discomfort and occasional mortality. The newer, more powerful and less toxic derivatives of the thiouracil group, as 6-propylthiouracil, safely break the “vicious cycle” of thyroid stimulation to lower the basal metabolic rate. The drugs of the thiouracil group have already been used in treating angina pectoris. In the small number of cases reported to date, results have varied. A limited number of patients were improved^{3,4,5} and others remained unchanged or even progressed.⁶ This report adds 10 cases to those previously reported so that it may be possible better to select those cases which may respond to thiouracil therapy.

METHODS

Ten hypertensive patients with a definite anginal syndrome were chosen. Typical precordial or substernal pain, usually related to exertion, had been present from five months to seven years. Only those patients who had been followed for many years in the clinic or hospital were included, so that the effect of the drug could be carefully evaluated. It was thought necessary to select these patients with care since in a condition such as angina pectoris, even though the coronary disease is one of progression, the pain is subject to spontaneous remissions despite the pathologic process already present. All patients had been previously treated with various medication, including placebos, without success. With the exception of thiocyanate therapy in some cases, and nitroglycerin when required, no medication other than propylthiouracil was given during the study.

Four patients had elevated basal metabolic rates, over 10 per cent, before treatment was started. This proportion of hypermetabolism in hypertension has been in accord with our experience in the Hypertensive Clinic where

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From the Hypertensive Service, Department of Medicine, The Jewish Hospital, Brooklyn, N. Y.

Propylthiouracil was supplied through the courtesy of Dr. S. M. Hardy, Lederle Laboratories, Inc., Pearl River, N. Y.

one third of over 200 cases have high metabolic rates.⁷ These patients gave no evidence of clinical hyperthyroidism and both the blood cholesterol and urine creatinine studies were within normal limits. The reported incidence of elevated basal metabolic rates in hypertensive patients with adequate cardiac compensation is 26.5 per cent.⁸ The blood cholesterol values in these four patients were not abnormal. No direct correlation was noted between the basal metabolic rate and the height of either the systolic or diastolic blood pressure.

Only one of the 10 patients was a male. This preponderance of females with angina pectoris is accounted for by the fact that 75 per cent of the patients in the Hypertensive Clinic are females. It is also possibly explained by the fact that women with angina pectoris tend to survive longer than men with the condition.⁹ The ages of the patients varied from 45 to 62 years. The severity and frequency of anginal pain were subjectively evaluated and graded as mild, moderate or severe. Patients were instructed to list the number and severity of attacks each day. At first the patients were seen every week, later every two weeks. A leukocyte and differential count were done at every examination. When possible, monthly determinations of the basal metabolic rate and blood cholesterol were made. Teleroentgenogram, electrocardiogram and fundusoscopic examinations were made at the beginning of treatment and repeated when necessary.

CASE REPORTS

The following cases are illustrative of the problems encountered during the trial period.

Case 4. A 62-year-old white man was first seen in 1944. His blood pressure was 220 mm. Hg systolic and 120 mm. diastolic. At this time he had occasional precordial pain on effort. During 1945 he was treated with potassium thiocyanate without relief and it was discontinued. His symptoms became progressively more severe with intense substernal distress referred to the neck and left shoulder, brought on by only slight effort. A teleroentgenogram showed normal lung fields with enlargement of the left ventricle. The electrocardiogram showed left axis deviation with evidence of myocardial abnormality. Fundusoscopic examination revealed advanced retinal vessel sclerosis. At the start of treatment the basal metabolic rate was minus 2 per cent, the cholesterol level 265 mg. per cent and free cholesterol 21 per cent. Propylthiouracil was given in dosage of 50 mg. twice a day. One month later the dose was increased to 150 mg. daily. After two months of treatment the basal metabolic rate was minus 27 per cent. There was no change in the intensity and frequency of pain. At this time the patient also complained of intermittent claudication and swelling of the legs. In spite of further propylthiouracil the substernal pain became more intense, was present even at rest. Treatment was discontinued after five months.

Comment: This was an instance of progressive angina pectoris, unaffected by propylthiouracil in large doses. The dose was sufficient to decrease the basal metabolic rate to low levels without affecting the anginal status. Intermittent claudication and a tendency to water retention occurred during treatment, probably as a result of the lowered metabolism.

Case 5. A 64-year-old white woman had been followed in the clinic since 1928. A basal metabolic rate in 1939 was plus 6 per cent. Substernal distress, radiating to the left shoulder, related to effort and only relieved by nitroglycerine had been present for four months previous to treatment with propylthiouracil. A teleroentgenogram revealed an enlarged cardiac shadow mainly in the region of the left ventricle. The electrocardiogram showed left ventricular preponderance, intra-ventricular conduction defect and slight myocardial abnormality. Funduscopic examination revealed sclerosis of the vessels. The basal metabolic rate was plus 20 per cent and the blood cholesterol was 231 mg. per cent with 27 per cent free cholesterol. Propylthiouracil was started with a dose of 100 mg. daily. One month later the basal metabolic rate was plus 25 per cent and there was no change in symptoms. After two months of treatment the basal metabolic rate fell to plus 7 per cent. Anginal pain was now less frequent and of a milder degree. Because of diaphoresis which the patient felt was due to the medication, the dose was decreased to 75 mg. a day; but later was increased again to 150 mg. daily. Angina was still present but to a much milder degree after 22 weeks of treatment.

Comment: This is an instance of moderate angina pectoris of recent origin which was slightly improved with propylthiouracil. The basal metabolic rate was depressed 18 points but still remained within normal limits.

Case 8. A 49-year-old colored woman with a previous history of lymphogranuloma venereum was found to have hypertension in 1943. At this time teleroentgenogram, electrocardiogram, funduscopic examination and intravenous pyelogram were negative. Precordial pain, radiating to the left shoulder and arm following exertion and excitement began in 1945. This became progressively more severe and the patient was forced to stop working in February, 1946. At this time a teleroentgenogram showed a boot-shaped, moderately enlarged heart with prominence of the left ventricle. The only abnormal electrocardiographic finding was left ventricular preponderance. Funduscopic examination revealed angiosclerosis and irregular caliber of the vessels. The basal metabolic rate was minus 8 per cent, while the blood cholesterol was 251 mg. per cent, with 30 per cent free cholesterol. The starting dose of propylthiouracil was 25 mg. three times a day. Five weeks later the basal metabolic rate had fallen to minus 22 per cent and the symptoms had improved to such an extent that the patient was now able to work several days a week as a maid. The dose was decreased to 50 mg. a day. The following month the basal metabolic rate was minus 20 per cent. At this time there was slight fatigue, swelling of the legs and increase in size of the thyroid gland. After seven months of treatment, with the smaller dose, the anginal pains were very infrequent and the patient was able to work an entire week.

Comment: This patient, incapacitated with severe angina, improved sufficiently within a two month period of treatment to return to work. She was well maintained on a low dose of 50 mg. a day. Evidence of water retention and thyroid gland enlargement was present.

Case 9. The patient, a 46-year-old white woman, was first treated in 1936 for hypertension. That same year a thyroid adenoma was removed. Mild substernal pain, with the typical distribution of angina pectoris, was noted in 1938. It was not relieved by medication other than nitroglycerin. A basal metabolic rate in 1942 was minus 2 per cent. Since 1945 she had been treated with potassium thiocyanate. At the time of starting propylthiouracil, the angina had slightly progressed and was classified as moderately severe. The basal metabolic rate was plus 26 per cent. A

teleröntgenogram was negative. The electrocardiogram showed left axis deviation. Fundusoscopic examination revealed tortuous vessels and arteriolar spasm. The blood cholesterol was 279 mg. per cent with 21 per cent free cholesterol. The initial dose of propylthiouracil was 25 mg. three times a day. Within one month effort tolerance had increased and no substernal pain occurred at rest. The basal metabolic rate was now plus 19 per cent. Her headaches recurred and potassium thiocyanate was again given. The dose of propylthiouracil was gradually increased to 150 mg. a day. After 33 weeks of treatment the basal metabolic rate had fallen to plus 6 per cent. Substernal pain rarely occurred and the patient was able to do her own housework for the first time in two years.

Comment: This patient with moderately severe angina pectoris of seven years' duration showed prompt and continued improvement with propylthiouracil. The basal metabolic rate dropped from plus 26 per cent to plus 8 per cent with moderate dosage.

Case 10. A 56-year-old white woman had been treated for hypertension since 1934. An intravenous pyelogram at that time showed a small hypoplastic right kidney. Substernal pain, radiating to the left shoulder and arm had been present since 1940, at which time the basal metabolic rate was plus 7 per cent. She complained of headaches which were relieved with potassium thiocyanate. Propylthiouracil was started with a dose of 25 mg. twice a day. The basal metabolic rate at this time was plus 21 per cent. The blood cholesterol was 271 mg. per cent with 26 per cent free cholesterol. A teleröntgenogram showed the chest and heart to be negative. The electrocardiogram revealed left ventricular preponderance. After two months of treatment only occasional substernal pain was present. The basal metabolic rate was still plus 20 per cent. The dose of propylthiouracil was gradually increased until 200 mg. a day were given. With six weeks of this dose, the basal metabolic rate fell to plus 10 per cent and the substernal pain completely disappeared.

Comment: This patient with substernal pain on effort for seven years received complete relief within two months. The dose of propylthiouracil which relieved the symptoms was insufficient to lower the basal metabolic rate. In spite of increasing the dose to 200 mg. a day, the basal metabolic rate remained within normal limits.

RESULTS

Of 10 patients with hypertension and angina pectoris who received 6-propylthiouracil, four patients showed definite symptomatic improvement (table 1). Two of the others, in one of which the basal metabolic rate fell to minus 27 per cent, became progressively worse. No correlation could be drawn between the improvement in symptoms and the level of the basal metabolic rate. Previously it had been thought that best results in these patients were obtained with a basal metabolic rate ranging from minus 10 per cent to minus 20 per cent, following thyroidectomy^{10, 11} or after thiouracil treatment.⁶ Di Palma expressed the opinion that with an initial basal metabolic rate of minus 10 per cent it was useless to give thiouracil in an effort to decrease symptoms. This statement cannot be accepted without reservation since one of the patients in this series, with an initial basal

TABLE I

Case No.	Patient	Sex	Age	Daily Dose of Propylthiouracil	Duration of Treatment	Initial BMR	Lowest BMR Obtained	Receiving Thiocyanate Treatment	Duration of Angina Pectoris	Severity of Pain	Result	Comment
1	C. G.	F	49	75 mg. 100 mg.	11 weeks 8 weeks	+10%	+10%	yes	4 years	severe	Unimproved	Swelling of the feet present
2	F. C.	F	57	100 mg. 150 mg.	8 weeks 4 weeks	+4%	-7%	yes	1 year	Mod. severe	Unimproved	
3	L. S.	F	45	100 mg. 150 mg.	10 weeks 8 weeks	+45%	+25%	no	1 year	Mod. severe	Unimproved	A possible case of masked hyperthyroidism
4	B. R.	M	62	100 mg. 150 mg. 75 mg.	4 weeks 4 weeks 13 weeks	-2%	-27%	no	2 years	severe	Unimproved	Intermittent claudication and swelling of the feet; symptoms progressed
5	B. R.	F	64	100 mg. 75 mg. 150 mg.	9 weeks 8 weeks 5 weeks	+25%	+7%	no	4 months	Mod. severe	Improved	
6	T. F.	F	61	75 mg. 150 mg.	9 weeks 5 weeks	-1%	-3%	yes	7 years	Mod. severe	Unimproved	Sleepiness and fatigue
7	M. G.	F	49	100 mg. 75 mg.	4 weeks 14 weeks	+3%	+7%	no	5 months	Mod. severe	Unimproved	Symptoms progressed Sympathectomy was done with relief of symptoms
8	W. S.	F	49	75 mg. 50 mg.	5 weeks 28 weeks	-8%	-26%	no	1½ years	severe	Improved	Swelling of the feet and enlargement of the thyroid gland
9	R. F.	F	46	75 mg. 100 mg. 150 mg.	22 weeks 5 weeks 6 weeks	+22%	+6%	yes	7 years	Mod. severe	Improved	Dyspnea
10	C. D.	F	56	50 mg. 75 mg. 100 mg. 200 mg.	8 weeks 12 weeks 4 weeks 6 weeks	+21%	+10%	no	7 years	severe	Improved	Dyspnea

metabolic rate of minus 8 per cent, obtained complete relief when the level was further depressed to minus 26 per cent.

It must be remembered that in three of the four patients who showed improvement, the basal metabolic rate was still within normal limits; but that all four patients had a fall in the basal metabolic rate of 11 to 20 points. This was also brought out by Raab,³ five of whose eight patients improved despite normal basal metabolic rates. The initial basal metabolic rate had no influence on subsequent results. As seen in the treatment of thyrotoxicosis, improvement in patients with angina pectoris took place within two to eight weeks of treatment. If at the end of this time, no improvement was shown, then neither further increase, nor continuation of the medication for as long as six months, was of any avail.

Treatment with propylthiouracil in these 10 cases had no effect on either the blood pressure or on symptoms secondary to the hypertension. This was to be expected since thyroidectomy in hypertensive patients with elevated metabolic rates lowers the basal metabolic rate, but has no effect on the level of the hypertension.¹² The electrocardiograms were not appreciably changed. Effects on the blood cholesterol level were unpredictable and no persistent inverse relationship was found between a fall in the basal metabolic rate and a rise in the cholesterol level.

Potassium thiocyanate had been given to six of these patients subsequent to the administration of propylthiouracil and continued in four of them at some time during the course of treatment. Despite the clinical impression as to the goitrogenic nature of potassium thiocyanate,¹³ the initial basal metabolic rate in all of these patients remained within normal limits, despite a daily dose of 0.35 gram (gr. vi). There was no relationship between the previous administration of potassium thiocyanate and the subsequent response to propylthiouracil.

This study demonstrates again the known refractory nature of the normal thyroid to thiouracil. The lower the initial metabolic rate, the more difficult it is to further depress the metabolism with this drug. Even with the comparatively large doses of propylthiouracil used (as high as 200 mg. a day) it was still not possible to get a basal metabolic rate less than normal in most cases. Astwood¹⁴ reported myxedema in normal persons following five months of therapy with thiouracil, so it is probable that much higher doses may depress a normal metabolic rate. What effect this will have on subsidence of symptoms in angina pectoris remains to be seen.

Severe signs of thyroid deficiency developed in only one patient. These consisted of lethargy, weight gain, and puffiness of the legs and face. In six others, while the basal metabolic rate was not particularly low at the onset of therapy, when the level was decreased, water retention occurred. This caused dyspnea, drowsiness and edema of the legs. Intermittent claudication which has been described in myxedema as due to diminution of the peripheral blood flow, occurred in one case.

CONCLUSION

Depression of the basal metabolic rate with 6-propylthiouracil relieved substernal pain in four of 10 cases of hypertension with angina pectoris for a six month period. The initial basal metabolic rate and the subsequent readings did not determine the final results. Myxedema levels were not necessary for relief of pain, since three of the four patients who were relieved of pain had basal metabolic rates within normal limits at the time symptoms were improved. If improvement did occur, it did so within eight weeks of beginning treatment. Several untoward effects of 6-propylthiouracil treatment were noted, namely a tendency to water retention and intermittent claudication. No toxicity with 6-propylthiouracil, in doses up to 200 mg. a day, was observed.

The ideal initial and maintenance dose of 6-propylthiouracil for the treatment of angina pectoris remains to be determined. If after adequate treatment for a two month period, there is no symptomatic improvement, further administration is probably useless. Since 6-propylthiouracil is relatively non-toxic and has shown benefit in some cases of angina pectoris, a further trial of its use is warranted.

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CHRONIC MELIOIDOSIS: DISCUSSION, CASE REPORT, AND SPECIAL STUDIES *

By LEONARD B. GUTNER, Captain, M.C., A.U.S., *New York, N. Y.*, and MYRON
W. FISHER, First Lieutenant, Sn.C., A.U.S., *Denver, Colorado*

MELIOIDOSIS is a rare disease which was first observed at autopsy in beggars in 1910 in Rangoon by Whitmore and Krishnaswami, and first reported in the literature in 1912.¹ Since the original account, several hundred cases have been so diagnosed, about 10 per cent of which were recognized during life. The disease is known to occur in a rather limited Oriental area, which includes Burma, Federated Malay States, Indo China, Ceylon, Thailand, Dutch East Indies, Singapore, Kuala Lumpur, China (Saigon), and, recently, two cases in U. S. Navy personnel on Guam.^{2, 3}

The causative organism, *Malleomyces pseudomallei* (also called *Pfeifferella whitmori*), produces a glanders-like disease which is fatal in approximately 95 per cent of cases within several days to four weeks.⁴ The course of the disease is that of an acute or subacute septicemia, which, on occasion, may be so fulminating and virulent as to cause death within 24 hours. The latter is the choleric or enteric variety, with severe vomiting, diarrhea, and peripheral circulatory collapse. The duration varies inversely with the dosage of organisms received and the extent of vital organ involvement. Multiple pyogenic abscesses are more likely to develop in the more protracted cases.

The admission complaints usually include a fairly sudden onset of malaise, non-productive cough, moderate fever, and occasionally, numerous superficial septic sores or subcutaneous abscesses.³ Pneumonia and acute pleuritis have been described. The chronic form may resemble tuberculosis, as did Mayer's case.⁵ Very rarely, the disease may evidence chronicity with multiple small discrete and large confluent sluggish abscesses of the various viscera or bones, with or without draining sinuses, dominating the clinical picture for months or years until death or cure supervenes. Only six such cases, including the present one, have been reported to this date.^{5, 6}

Pathologically, minute abscesses, which may coalesce, are found in the lungs, liver, spleen, kidneys, prostate and lymph glands, in that order of frequency.³ The lesions are definite granulomata with a central necrotic core of blood-stained "anchovy sauce pus," containing polymorphonuclear and mononuclear leukocytes, around which are round cells and a hemorrhagic periphery. The typical bipolar-staining organisms may be seen intra- and extra-cellularly.

Human infection probably occurs following the ingestion of water or food contaminated by the sputum, urine, or feces of infected rodents, among which the disease is known to be quite prevalent in the areas previously named. The

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From the Laboratory Service of Col. Hugh W. Mahon, M.C., and the Medical Service of Colonel Charles B. Kendall, M.C., United States Army, Fitzsimons General Hospital.

possibility of direct or indirect insect vector transmission to man exists, because the rat flea is known to harbor and allow the multiplication of the organism, and the *Aedes aegypti* mosquito can be infected.⁷ Rats, cats, dogs, guinea pigs, rabbits and monkeys are easily infected, but equines are apparently immune.⁸ Man does not appear to be readily susceptible to the disease, as is evidenced by its rarity in man in endemic areas which are notorious for large rodent populations and overcrowded, squalid living conditions. Susceptible animals may be infected by the oral, parenteral, or intraperitoneal routes, or simply by inoculation of the organism or infected material upon the unbroken skin.

There is no known specific therapy, and a tendency toward spontaneous remission in the recorded chronic cases makes evaluation of any treatment uncertain. From the point of view of good surgical management, abscesses should be drained early and adequately. Sulfonamides have been reported to be of value in that they will lower the temperature and diminish the malaise, but the abscesses are not eradicated.⁶ Penicillin and autogenous vaccines have been employed with little or no success; and streptomycin, which has not been used in this disease to date, is worth trial if the particular strain of the organism is sensitive to practicable concentrations in vitro. This strain was inhibited only by a concentration of 125 mcg. of streptomycin per ml. Urea has been reported as being bactericidal to the organism in vitro, but was of no demonstrable value in one case.⁵

Finally, it may be stated that the bacteriological diagnosis from sputum, urine, blood, discharges, or biopsy is the only reliable one.

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History: Patient is a 25 year old white male, with a past history of four attacks of right-sided pleuritis, the last occurring in 1940. In July 1944, while in the Army, he was hospitalized in Hawaii for an appendectomy, and five weeks later underwent a laparotomy for an abscess of a Meckel's diverticulum.

The present illness began in Dagupan, Luzon, P. I., when the patient was admitted to the 37th Station Hospital on July 30, 1945 for a hemorrhoidectomy and complaints of post-prandial nausea and vomiting and 45 pounds weight loss during the year following his aforementioned abdominal operations. The hemorrhoidectomy was performed shortly after admission; and the patient did well post-operatively until August 11, when acute gastrointestinal symptoms appeared, and later, during the same day, acute right lower anterior chest pain, splinting of the affected side, and a fever of 102.4° F. Roentgen-rays revealed a right lower lungfield haziness which progressed to an obvious pleural effusion. The white blood count at that time was 18,800 with 76 per cent polymorphonuclear leukocytes.

On August 15, 60 ml. and 450 ml. of straw-colored fluid were aspirated from the right chest and proved to be negative bacteriologically on smear and culture. A third aspiration on August 19 produced 30 ml. of thin yellow fluid containing a few fibrin strands, following which 100,000 units of penicillin were injected intrapleurally. Therapy included parenteral penicillin, oral sulfadiazine, oxygen, intravenous fluids, and large frequent doses of codeine and morphine for very severe right chest pain. The specific treatment had no demonstrable salutary effects on the symptoms, the clinical findings of a right pleural effusion, or the temperature, which lytically dropped to normal about September 3. The elevated white blood count and accompanying polynucleosis persisted, varying from 16,150 to 22,200 with 70 to 88 per cent polymorphonuclear leukocytes.

He was evacuated to the United States still complaining of continuous severe right chest pain aggravated by a dry hacking cough. On September 5, nausea, vomiting and night sweats occurred, and a fever of 103.8° F. was recorded. Following this flare-up, he had an intermittent low-grade fever for the next seven months, during which time three courses of penicillin and one short period of oral sulfadiazine administration failed to alter a slowly downward clinical picture. The weight fell to 60 pounds below the patient's average; and anorexia, frontal headaches, sweats, severe right chest pain and a nauseating, distressing non-productive cough with occasional emesis persisted. Numerous sputa, gastric lavages, and 1 ml. of purulent material aspirated from the right chest on January 21, 1946 were negative for acid-fast bacilli on smear and culture. Blood counts continued to exhibit a leukocytosis and a polynucleosis, and corrected sedimentation rates ranged from 28 to 40 mm. per hour. Roentgen-rays revealed a gradual clearing of the effusion, but the right diaphragm was persistently elevated and fixed to the right lateral chest wall, and the pleura between the right middle and lower lobes was thickened.

The cough eventually became productive of a half to one and a half ounces of foul purulent sputum daily, and pallor and mild to moderate clubbing of the fingers and toes developed. Bronchoscopy in the early spring of 1946 revealed a shaggy inflamed right bronchial mucosa, with a mucopurulent exudate, especially in the middle and lower lobe areas. Because of the diagnosis of chronic suppurative pulmonary disease, a rib resection was recommended to forestall the possible development of a broncho-pleural fistula, but was not carried out because of the marked improvement which set in following the coughing up of a large bronchial plug on April 25.

On June 22, a large lymph node was noted at the angle of the left side of the mandible; and a heterophile antibody reaction nine days later was two plus in 1:224 dilution, but was completely absorbed by guinea pig kidney antigen. On July 11, the patient was admitted to Fitzsimons General Hospital appearing acutely and chronically ill, weighing 145 pounds (average weight was 185 pounds), and complaining of intermittent right lower antero-lateral chest pain, worse on coughing and deep breathing, weakness and anorexia, but no sore throat.

Physical Examination on Admission: The tongue was coated and the breath was foul. A warm, tender fluctuant mass, measuring 4 to 5 cm. in diameter, was present just below the angle of the left side of the mandible. The right lower chest lagged during inspiration, and dullness, diminished breath sounds, and essentially normal vocal fremitus were found over the right lower third posteriorly and in the axilla. The spleen was not palpably enlarged, but fist percussion over the lower left ribs, anteriorly and posteriorly, elicited some tenderness. The liver edge was palpable just below the costal margin. Moderate clubbing and cyanosis of the fingers and toes were present.

Course in the Hospital: On July 15, 5 ml. of thick, purulent, slightly blood-streaked material was aspirated from the fluctuant left neck mass, which on culture yielded what was apparently a species of *Alcaligenes*, but, in view of later results, was probably *Malleomyces pseudomallei*. Because of the spreading nature of the abscess area, an incision and drainage was performed on July 23 and about 30 ml. of pus evacuated. On August 8, one left axillary and bilateral inguinal and femoral lymph nodes were noted to be enlarged, and a tender firm splenic edge was palpated two and a half fingers' breadth below the left costal margin in the mid-clavicular line. The lymphadenopathy receded in three weeks, but the spleen remained unchanged in size though the tenderness gradually diminished.

The patient gradually improved following the incision and drainage; but a continuously draining sinus persisted despite the prolonged administration of parenteral penicillin in beeswax-oil and local penicillin irrigations daily; and pigmentation and keloid-like scarring gradually appeared about the sinus orifice. Culture of this drain-

age material was negative on nine occasions for acid-fast bacilli and in 10 instances for fungi; and cultures every third day for pyogens revealed, on two occasions, gram-negative bacilli that were relatively biochemically inert. These were again thought to be a species of *Alcaligenes* or *Pseudomonas*, but in retrospect were probably *M. pseudomallei*. Hemolytic *Staphylococcus aureus* was consistently present in abundance in these specimens as a secondary invader, so that the presence of *M. pseudomallei* was probably obscured.

On October 30, a complete excision of the left neck suppurative node was accomplished. The contents of this node were negative on smear, but routine culture revealed abundant pure growth of a small, gram-negative, bipolar-stained bacillus which was identified after extensive bacteriological study as *Malleomyces pseudomallei*. Then, for the first time, the diagnosis of chronic melioidosis was established. The excision site healed quickly and drainage did not recur. On November 16, the patient left this hospital on a two weeks' convalescent furlough; and, while at home in Oregon, suddenly became acutely ill on November 28 and coughed up bile. He was hospitalized at a Veteran's hospital in Portland and treated with penicillin and streptomycin. He was operated on three times, the exact natures of which are unknown, and a diagnosis of broncho-biliary fistula was made, probably secondary to a liver abscess which had invaded the pleural cavity. Specimens of blood and sputum were mailed to Fitzsimons General Hospital on December 23. Blood culture was negative after two weeks of incubation, but *M. pseudomallei* was recovered after intraperitoneal injection of sputum into a male guinea pig, which manifested the Straus reaction in four days. The patient returned to Fitzsimons General Hospital for further observation and treatment.

Laboratory Data: The white blood count on July 19, 1946 was 23,700 with 74 per cent polymorphonuclear leukocytes. This rose to a peak on August 6 of 25,000 with 68 per cent neutrophils, and then gradually fell to 15,200 with 53 per cent neutrophils and 7 per cent eosinophils on November 14. No significant lymphocytosis or any abnormal lymphocytes were ever noted. A sternal puncture biopsy revealed slight hyperplasia with an increase in the segmented forms and numerous eosinophils, with the over-all picture suggestive of suppurative infection. The sedimentation rate was persistently elevated above 22 mm. per hour; and a Frei test, done because an inguinal node biopsy was suggestive of lymphogranuloma venereum, was negative. A gastrointestinal series and a barium enema were negative radiographically. Bronchograms were normal except that the right lower lobe appeared much reduced in size and the middle lobe either could not be filled or was indeterminate.

Heterophile antibody reactions are reported below in detail because of the possibility of their being false positives. No absorption tests were done.

July 18, 1946	—negative	October 2	—positive 1:256
July 30	—positive 1:512	October 5	—positive 1:128
August 7	—positive 1:1024	October 12	—negative
August 14	—positive 1:1024	October 19	—negative
August 21	—positive 1:1024	October 26	—negative
August 30	—positive 1:128	November 6	—positive 1:256
September 7	—positive 1:128	November 9	—positive 1:256
September 10	—positive 1:128	November 16	—negative
September 14	—negative		
September 24	—positive 1:256		
September 28	—positive 1:128		

Pathological Reports: (1) Left inguinal node biopsy on August 30, 1946. The general architecture of the node was unaltered, but the follicles were prominent and varied from distinct germinal centers to proliferation and invasion by surrounding

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lymphocytes. The sinuses were dilated and contained numerous reticulo-endothelial cells, and some congestion was present. The picture was suggestive, but not typical, of infectious mononucleosis.



FIG 1. Multiple necrotic areas in cervical lymph node with surrounding granulomatous reaction. $\times 300$.

(2) Left cervical node excision biopsy, October 30, 1946. One section of the slide revealed distortion by broad, interconnecting bands of dense, relatively acellular fibrous tissue. Large abscess cavities were present in the central lymphoid portions, many having a stellate, streaked, or oval configuration with central solid masses of polymorphonuclear leukocytes, and were surrounded by a zone of reticulo-endothelial cells having relatively large vesicular oval to irregularly shaped nuclei. About this

marginating zone was a collar of lymphocytes and plasma cells (figure 1). Other areas revealed a more definitely granulomatous aspect with epithelioid cells and some questionable giant cells (figure 2).

(3) Guinea pig autopsy on December 3 following intraperitoneal injection with macerated portions of the above described cervical lymph node. The mesenteric



FIG 2 Granulomatous reaction in cervical lymph node, predominantly epithelioid. $\times 300$.

lymph nodes were grossly enlarged, and, on section, appeared composed of pale grayish-white cheesy material enclosed by a thin capsule. Microscopically, the normal nodal architecture was completely obliterated and the eosin-staining debris was heavily infiltrated with polymorphonuclear leukocytes (figure 3) Gram-picric stains revealed occasional aggregates of bacillary forms

Grossly, the liver presented linear gray streaks; and, microscopically, a few areas of degeneration with debris and small clear spaces (fat) without caseation. Micro-

scopically, the spleen was studded with numerous small gray opaque follicular areas; and, microscopically, these showed central necrosis ringed by epithelioid cells. Diagnosis: Focal necrosis of liver and spleen with suppurative mesenteric adenitis.

Bacteriological Studies: The organism which was isolated from the biopsied left cervical node was a small, pleomorphic, gram-negative bacillus showing bipolar



FIG. 3. Multiple granulomata with necrotic centers in guinea pig mesenteric lymph node.
X 25.

staining (figure 4). No acid-fast properties were demonstrable. A capsule was evident only in smears made of exudates from infected guinea pigs. Active motility was observed in semi-solid agar and tryptosephosphate broth in 24 hours, both at room temperature and 37° C. This bacillus grew abundantly on the usual laboratory media, as EMB, MacConkey's, Hajna's TSI, and blood agars; however, it failed to grow on SS agar (Difco). On EMB agar, the colonies were at first colorless, but within three

days assumed a light bluish color. On MacConkey's agar, growth was at first light pink, but deepened to bright red after four days. On 5 per cent glycerol agar, growth in the first 24 hours at 37° C. consisted of small, smooth, opalescent colonies, which, at the end of 72 hours' incubation, became opaque with a light yellow-brown chromogenesis. When first isolated (from the cervical node), this organism yielded only smooth growth on this agar, but after passage through guinea pigs, the highly wrinkled growth typical of the virulent phase of *M. pseudomallei* was evident (figure 5). On human blood agar, there was slight hemolysis in 24 hours, and complete clearing after three additional days of incubation. On tryptose agar, colonies had an oily, metallic sheen. In nutrient broth, a heavy surface pellicle was formed and a



FIG. 4. Typical bipolarly stained bacilli. $\times 2700$.

slimy tenacious sediment accumulated, with evenly distributed turbidity. All cultures emitted a strong, penetrating mouldy odor. Anaerobically, there was only scant growth in four days of incubation.

Gelatin was completely liquefied within five days at 37° C.; there was slight liquefaction of Loeffler's blood serum slants after seven days. Negative biochemical results were obtained for: indole, urease, MR-VP, and hydrogen sulfide. Citrate was utilized, and nitrates were reduced. The following carbohydrates were fermented with the production of a small amount of acid without gas: glucose, glycerol, and levulose in three days; mannitol, sorbitol, inositol, xylose, and maltose in 10 days; and sucrose, lactose, and dextrin in 22 days.

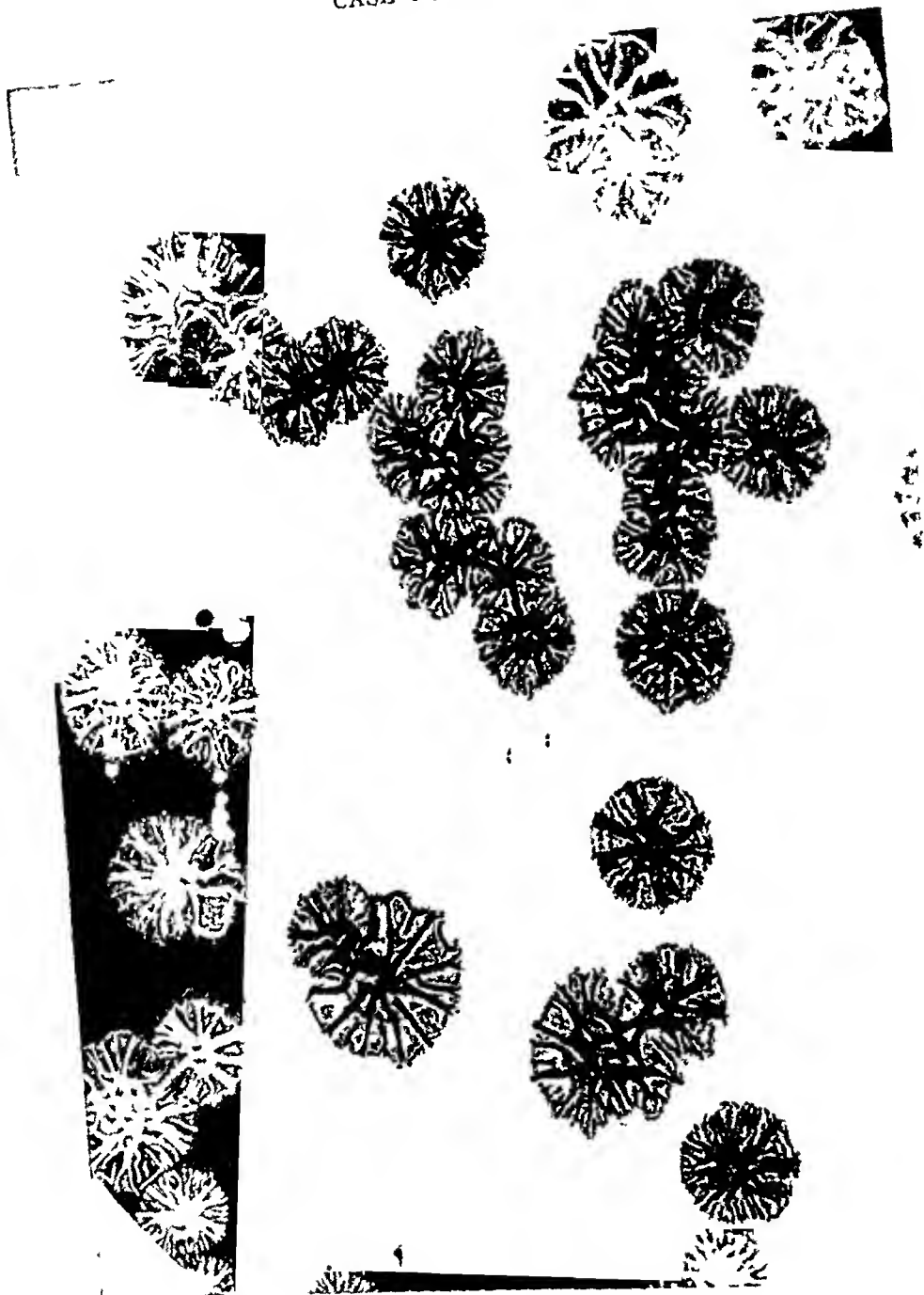


FIG. 5. Highly wrinkled colony growth of *M. pseudomallei*. $\times 4$.

Four adult male guinea pigs, each of which had been inoculated with infected material from the patient or a pure culture of the organism, developed a typical Straus reaction with gross enlargement and inflammation of the scrotum within three to five days. On opening the scrotum, a thick, cheesy, yellowish-white exudate was seen between the visceral and parietal layers of the tunica vaginalis; and, microscopically, these layers exhibited an acute inflammatory reaction (figure 6). The testis itself was essentially free of any such inflammatory response. The four guinea pigs died after 5, 11, 18 and 20 days, the variation in time being due to the variation in the number of organisms in the infecting dose. The causes of death were septicemia and diffuse suppurative lesions.



FIG. 6. Straus reaction with inflammatory reaction in visceral and parietal layers of the tunica vaginalis. $\times 75$.

Serological Reactions: (1) A culture of this organism was sent to the Army Medical School, Washington, D. C.; and, there, was agglutinated in a dilution of 1:320 with a specific antiserum prepared from a virulent strain of *M. pseudomallei*, and in a dilution of 1:640 with an avirulent strain antiserum. There was partial agglutination with both antisera up to, and including, a dilution of 1:1280.

(2) The patient's serum agglutinated a suspension of this organism up through a dilution of 1:2560.

The cultural, pathological, and serological studies previously described identify this organism as *Malleomyces pseudomallei* (Whitmore).⁹

CASE DISCUSSION

The isolation of this unusual bacillus outside of its fairly sharply-demarcated Oriental habitat must be regarded as an extraordinary event; for *M. pseudomallei* would be the last organism incriminated, particularly in a grossly atypical clinical case. This is the first recorded isolation and identification of this organism in the Western Hemisphere, and is the first report of a case of melioidosis contracted in the Philippine Islands. We must assume that it was carried to the United States from Luzon in a somewhat avirulent and attenuated state in the lungs and lymph glands of this patient. We are led to the further assumption from this case report that either there is a generalized seeding of the organism at the time of initial infection, with some of these foci becoming quiescent, only to be reactivated at some later date; or that the primary focus, in this case the lungs, may be the source of future dissemination throughout the body. If the latter is true, then there is a great similarity between the chronic phase of this disease and tuberculosis, coccidioidomycosis, etc.

The lymphadenopathy and splenomegaly presented by this patient at first appeared to be on the basis of infectious mononucleosis. However, in spite of the persistently positive Paul-Bunnell tests in high dilution, neither a lymphocytosis nor any atypical lymphocytes were ever demonstrated. Further evidence against the presence of infectious mononucleosis is the occurrence in this case of suppurative adenopathy, which either is not reported in the literature as being a part of infectious mononucleosis, or is extremely rare.^{10, 11, 12, 13, and 14} Then, the lymphadenopathy which occurs in infectious mononucleosis is primarily the result of a local process causing predominant symptoms in local lymph nodes draining the infected area.¹⁵ In this case, there was never any clinical evidence of pharyngitis, tonsillitis, otitis or rhinitis which could form a nidus from which drainage could reach the left upper anterior cervical lymph nodes.

On the other hand, it must be remembered that the bone marrow in infectious mononucleosis is responsively normal and fully capable of reacting to local supuration with a leukocytosis and a polynucleosis, even to the point of overshadowing or obliterating a preëxisting abnormal lymphocytosis.¹⁶ But, for a reliable diagnosis to be made, some few of the Downey types I to III atypical large lymphocytes should be present in the peripheral blood.¹⁰

Therefore, we are left with the conclusion that either melioidosis is another disease entity which may give rise to a false positive heterophile antibody reaction, or that there was a coincidental infectious mononucleosis infection which occurred during the course of chronic melioidosis.

SPECIAL STUDIES

After the diagnosis was confirmed, it was decided to run some sensitivity studies on this organism to streptomycin, penicillin, sulfadiazine and urea, separately and in combination, in an effort to find the best possible therapeutic approach to the disease, exclusive of adequate surgical drainage of the abscesses. The medium used was 1 per cent Trypticase (Baltimore Biological Laboratories) in physiological saline. The test inoculum consisted of about 150,000 organisms of an 18 hour broth culture per ml. of medium. All tests were incubated at 37° C. and read at the end of 24 hours.

The results were as follows: (1) 125 micrograms of streptomycin per ml. was the minimum inhibitory concentration, a therapeutically unobtainable blood level. (2) This organism was strongly resistant to penicillin, and grew in the presence of 1,000 units per ml. (3) Similar resistance was found with sulfadiazine, with growth occurring in the presence of 1,000 milligrams per cent. (4) Urea in a concentration of 1,000 milligrams per cent also failed to inhibit growth. (5) There were no enhancing or synergistic effects obtainable by various combinations of two or more of the above four substances.

In summary, then, we may say that this strain of *M. pseudomallei* probably cannot be suppressed clinically by any combination of the usual chemotherapeutic or antibiotic drugs in general use at the present time. This statement is well borne out by the lack of clinical response of this case to any therapy except basic surgical principles.

SUMMARY

A case of chronic melioidosis is presented with an 18 month history up to the present writing, and with known involvement of the lungs, spleen, lymph nodes, and, probably, liver. It was pointed out that the possibility exists that this disease may be the source of false positive heterophile antibody reactions. Therapeutically, the strain of *M. pseudomallei* involved is resistant to streptomycin, penicillin, sulfadiazine, and urea in vitro, alone or in various combinations, within the limits of even remotely practicable blood levels.

ADDENDUM

Additional follow-up on this patient revealed that other lymph nodes have since enlarged and a large abscess appeared on the buttocks, all of which foci have yielded cultures positive for *M. pseudomallei*. As of November 1947, the patient was alive, and the veteran's hospital at Portland, Oregon, reported a temporary arrest of the morbid process.

After this case report was submitted for publication, a prior case report of chronic melioidosis appeared in the Jr. Am. Med. Assoc., May 24, 1947.

ACKNOWLEDGMENT

The authors wish to express their thanks to Colonel Hugh W. Mahon, M.C., Chief of Laboratory Service, for his very helpful criticism and advice; and to Majors Arthur Steer and Nelson S. Irey, of the Laboratory Service, for furnishing the pathological analyses.

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MULTIPLE MYELOMA WITH SPINAL CORD COMPRESSION AS THE INITIAL FINDING*

By LEOPOLD J. SNYDER, M.D., and SEYMOUR K. WILHELM, M.D.,
Eloise, Michigan

PLASMA cell myeloma causing spinal cord compression has occasionally been reported. Klemme¹ in 1933 reported five cases which he had observed in a three year period. Paul and Pohle² found 14 cases of myeloma of the spine in 45 cases of solitary myeloma of bone, whereas Pasternack and Waugh³ noted that four of 30 cases of solitary myeloma of bone occurred in the spine. Denker and Brock⁴ point out that many myelomas begin in a vertebral body and "announce their presence by compression of the cord." These authors go on to state that "typically the case is in a person in the fifth or sixth decade of life rapidly developing signs of transverse myelitis with manometric block." Usually the lesion is in the thoracic spine.

These and other authors^{1, 5} state that laminectomy will show a gray or reddish-gray mass pushing the cord posteriorly or encircling it. It is our desire to emphasize their statement that frequently laminectomy and removal of all or part of the extradural mass decompresses the cord. This procedure followed by local deep x-ray therapy frequently allows a patient bedridden with paraplegia to arise and resume his previous occupation for a significant period of time.

CASE REPORT

The patient, T. R., a 49 year old factory worker, entered the Wayne County Hospital and Infirmary with the chief complaints of numbness and tingling of the feet and trouble controlling his legs. The onset of his difficulties was sudden. About

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From the Medical Department of the Wayne County General Hospital and Infirmary, Eloise, Michigan.

four weeks before his admission to the hospital, the patient noted difficulty on arising one morning. Aside from some "electric treatments" by his local physician, he received no significant treatment; and due to the rapid progression of his complaints, he was advised to enter the hospital.

His past history was essentially that of good health except for receiving alternate hip and arm "shots" for one year because of "bad blood."

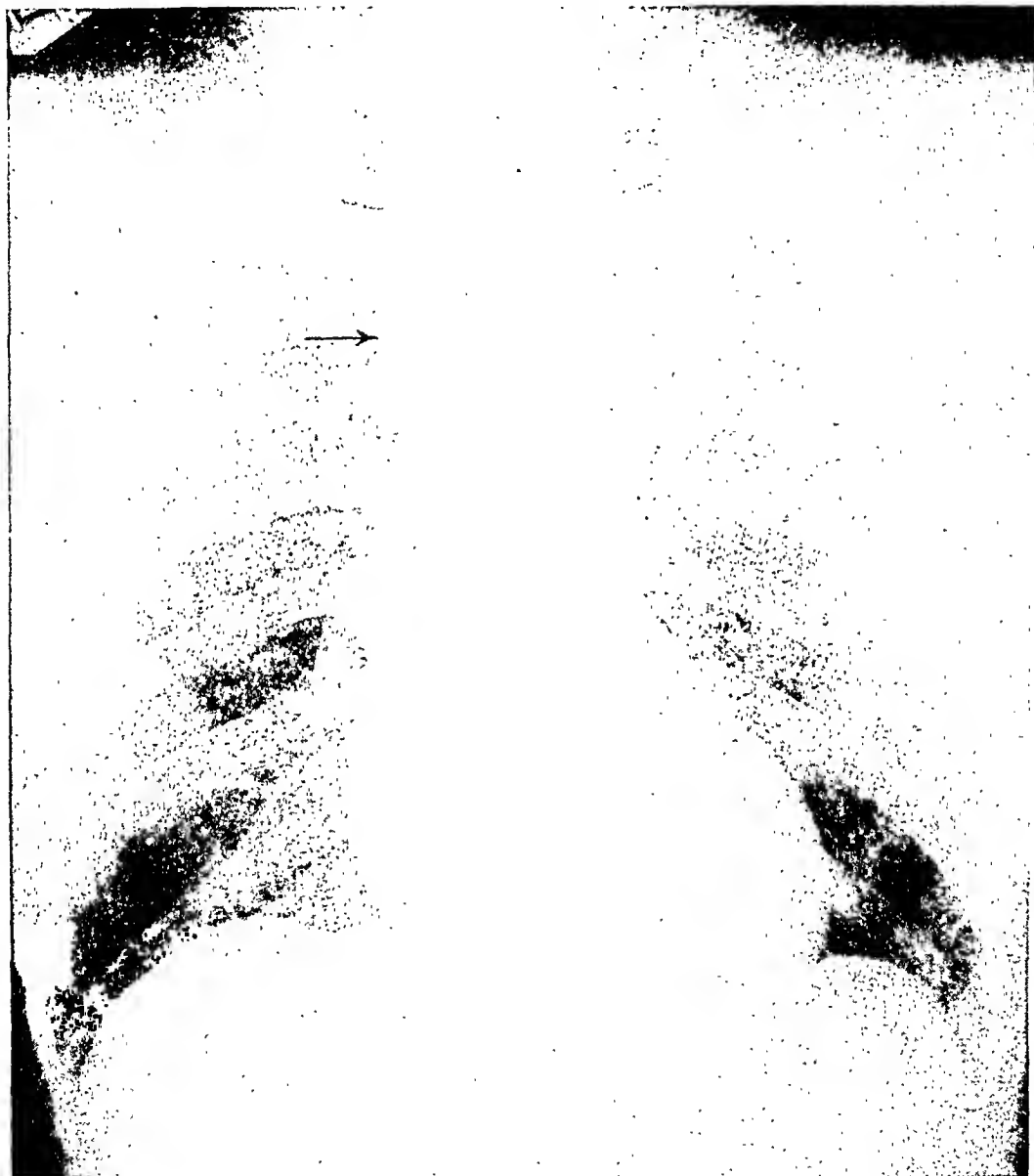


FIG. 1. Postero-anterior view of chest showing myeloma mass in right upper mediastinum. Initially interpreted as hilar lymphadenopathy.

Physical examination at the time of admission to the hospital revealed a well nourished and well developed negro male, not appearing acutely or chronically ill. Aside from his neurological findings, his physical examination revealed only poor oral hygiene and a soft rather low pitched apical systolic murmur. His temperature, pulse and respirations were normal; his blood pressure 140 mm. mercury systolic and 90 diastolic.

CASE REPORTS

Neurological examination revealed the cranial nerves to be intact. The reflexes in the upper extremities were entirely physiological. The abdominal reflexes were absent bilaterally, while the patellar reflexes were hyperactive and the achilles reflexes could not be elicited. No pathological reflexes were found. There was generalized weakness of all lower extremity muscle groups. The sensory examination revealed absence of testicular and calf pain following deep pressure. There was

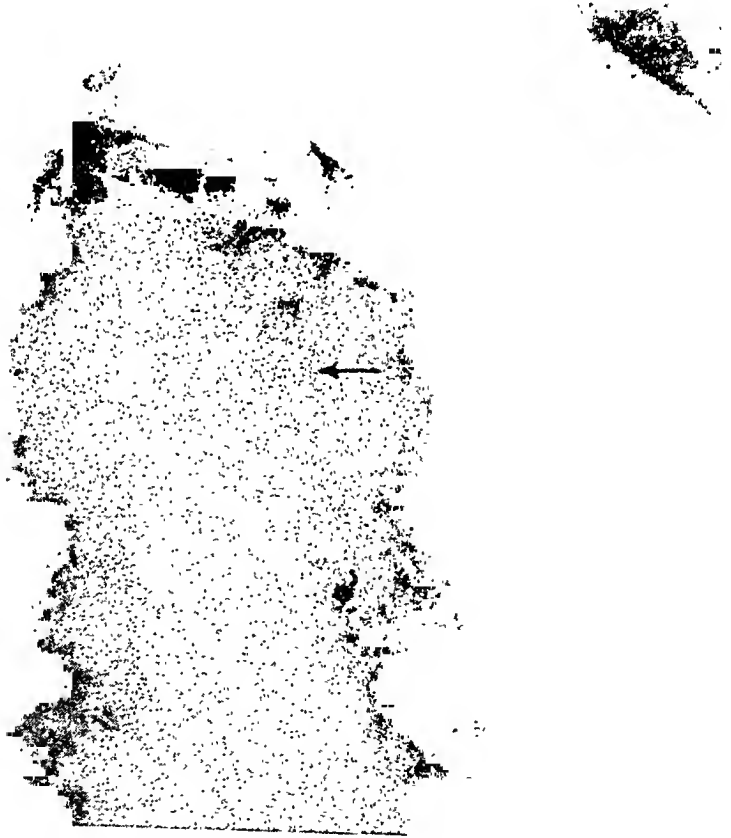


FIG. 2. Roentgenogram showing destruction of right pedicle of T₄ with soft tissue mass.

absence of vibratory perception and of sense of motion and position in the lower extremities; and it was felt that there was reduction to pinprick sensation up to the level of the mid thigh and low buttocks bilaterally. The gait was wide based, but evaluation of the Romberg test or coordination was made difficult by the weakness present.

The provisional diagnoses were spinal cord tumor or central nervous system syphilis.

The following day a lumbar puncture was done which revealed a clear, colorless

spinal fluid. The manometric readings showed an initial pressure of 220 mm. of water which, on left jugular pressure, rose to 350 mm. and then returned slowly to 290 mm. Right jugular compression caused a rise to 510 mm. with a smooth fall to 280 mm. Pressure on both sides caused a rise to 600 mm. of water. The spinal fluid on examination showed three white blood cells and two red blood cells, a 2 plus albumin and 2 plus globulin, the total protein being 118 mg. per cent and the Lange colloidal gold curve being 55555320000. The spinal fluid Kahn test was negative. Additional



FIG. 3. Air myelogram. Lateral view showing block at T₄.

laboratory examinations revealed a normal blood count, and urinalysis, and a negative blood test for syphilis.

Roentgenograms of the thoracic and lumbar spine at the time of admission showed what was interpreted as an old compression fracture in the body of the fourth thoracic vertebra with about 8 mm. of foreshortening at the anterior border of this same vertebral body. There was no definite evidence of bone destruction or dislocation. A posterior anterior roentgenogram of the chest (figure 1) showed a nodular shadow

at the right side of the upper mediastinum which was interpreted as hilar lymphadenopathy.

During the next few days, the patient's sensory level loss seemed to go higher. Dr. Russell T. Costello, the consulting neurologist, localized the sensory level at about the sixth thoracic vertebra. He believed that this patient's symptoms were most likely due to neuronitis of the Guillain-Barré type. He felt, however, that since the sensory level was so close to the site of a compressed vertebra, a spinal cord tumor had to be ruled out. He recommended myelography.

The lumbar puncture was repeated six days later. At this time the cell count was negative and the total protein had fallen to 80 mg. The gold curve was 5555321000, the first three 5s being atypical. The fall in total protein was interpreted as possibly meaning improvement in a neuronitis. The patient was cheerful and claimed improvement, though examination showed little change except for the development of a positive Mendel-Bechterew sign on the right.

Further roentgen-ray studies of the thoracic spine on April 18, 1946 (figure 2) showed an area of bone destruction involving the pedicle of the right side of the fourth thoracic vertebra. There also appeared to be a soft tissue density arising at the margin of the area of destruction. The previously noted compression of the body of the fourth thoracic vertebra was again noted. A lateral roentgenogram of the chest at this time revealed the shadow, previously interpreted as lymphadenopathy, to be identical with the soft tissue mass mentioned above. The roentgenologist's impressions were (1) neurofibroma or (2) metastatic malignancy in the region of the fourth thoracic vertebra.

On April 22, an air myelogram (figure 3) was done which revealed an incomplete block at the level of the fourth thoracic vertebra with a shift of the spinal cord to the left. Another lumbar puncture was done which showed no change in the fluid aside from a fall in the total proteins to 68 mg. per cent. Manometric readings at this time showed an initial pressure of 160 mm. of water. Right jugular pressure caused rise slowly to 250 mm. with a smooth slow fall to 180 mm. on release. Left jugular compression gave a slow smooth rise to 260 mm. with a slow fall to 210 mm. and then a very slow and gradual fall to 200 mm. Pressure following withdrawal of fluid was not recorded.

In view of the possibility of metastasis to bone, a urologic consultation was requested to rule out primary malignancy of the genito-urinary tract. Aside from cystoscopic evidence of a chronic cystitis and some blunting of the left pelvic calyces demonstrated by retrograde pyelography, no significant abnormality was found. There were many red blood cells in the urine from both ureters, but repeated urine smears and cultures were negative for tubercle bacilli.

Naffziger's test (figure 4) showed evidence of incomplete spinal block.

The patient was transferred to the neurosurgical service on April 30. He was almost completely bedridden. His lower extremities showed some muscle atrophy and his sensory level to pin prick was at the level of the xiphoid cartilage. The diagnosis on transfer was "extradural neoplasm at the level of the fourth thoracic vertebra with partial compression of the spinal cord."

On May 9, Dr. Aage Neilsen performed a laminectomy, removing the spinous processes of the third and fourth thoracic vertebrae. It was noticed that the laminae were infiltrated with a soft grayish tumor mass which extended to and was pressing on the spinal cord. Frozen section done during the operation was reported as "malignancy, probably carcinoma." Most of the tumor mass was removed, but it was the opinion of the operator that the tumor itself probably extended entirely around the spinal cord since there had been roentgen-ray evidence of involvement of the vertebral body. The tumor was not attached to the dura, being freely removeable except in its most anterior location. The dura was not opened.

The microscopic diagnosis (figures 5a and 5b) of the tissue removed at operation, was plasma cell myeloma in bone.*

A skull roentgen-ray (figure 6) later showed a few "punched out areas" in the left frontal and parietal bones. Bone marrow biopsy showed on direct smear 36 per cent plasma cells. The sedimentation rate was 115 mm. per hour (Westergren). No

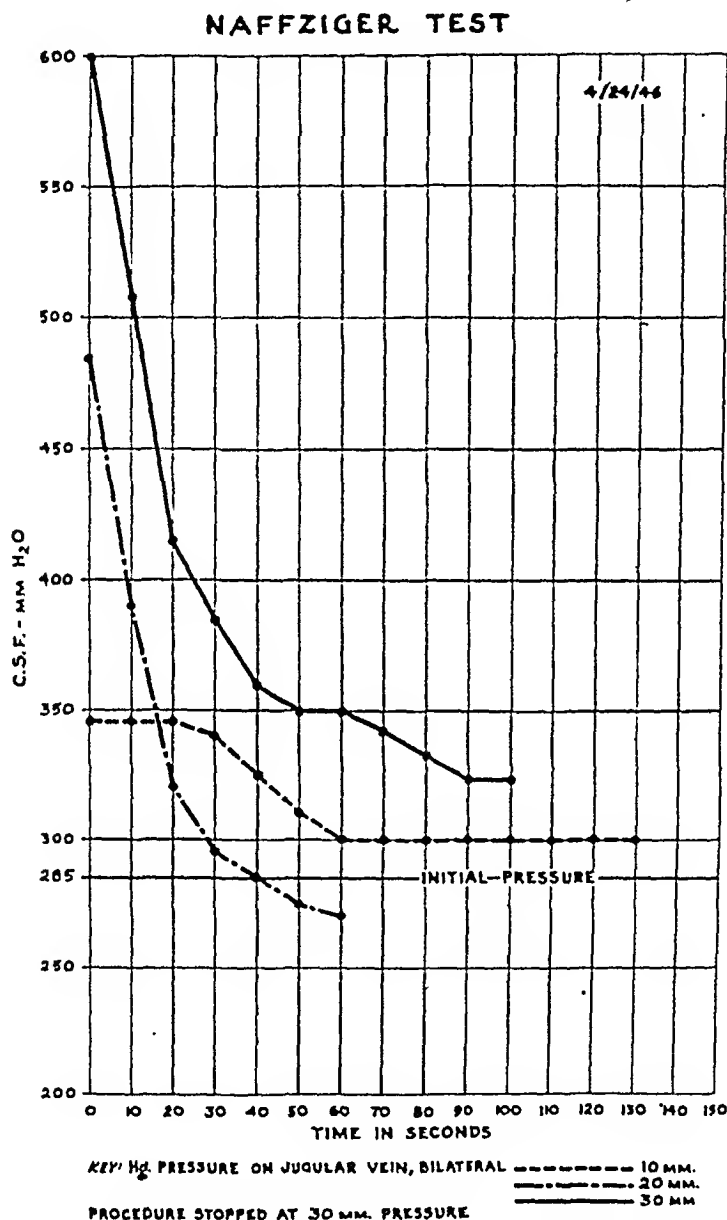
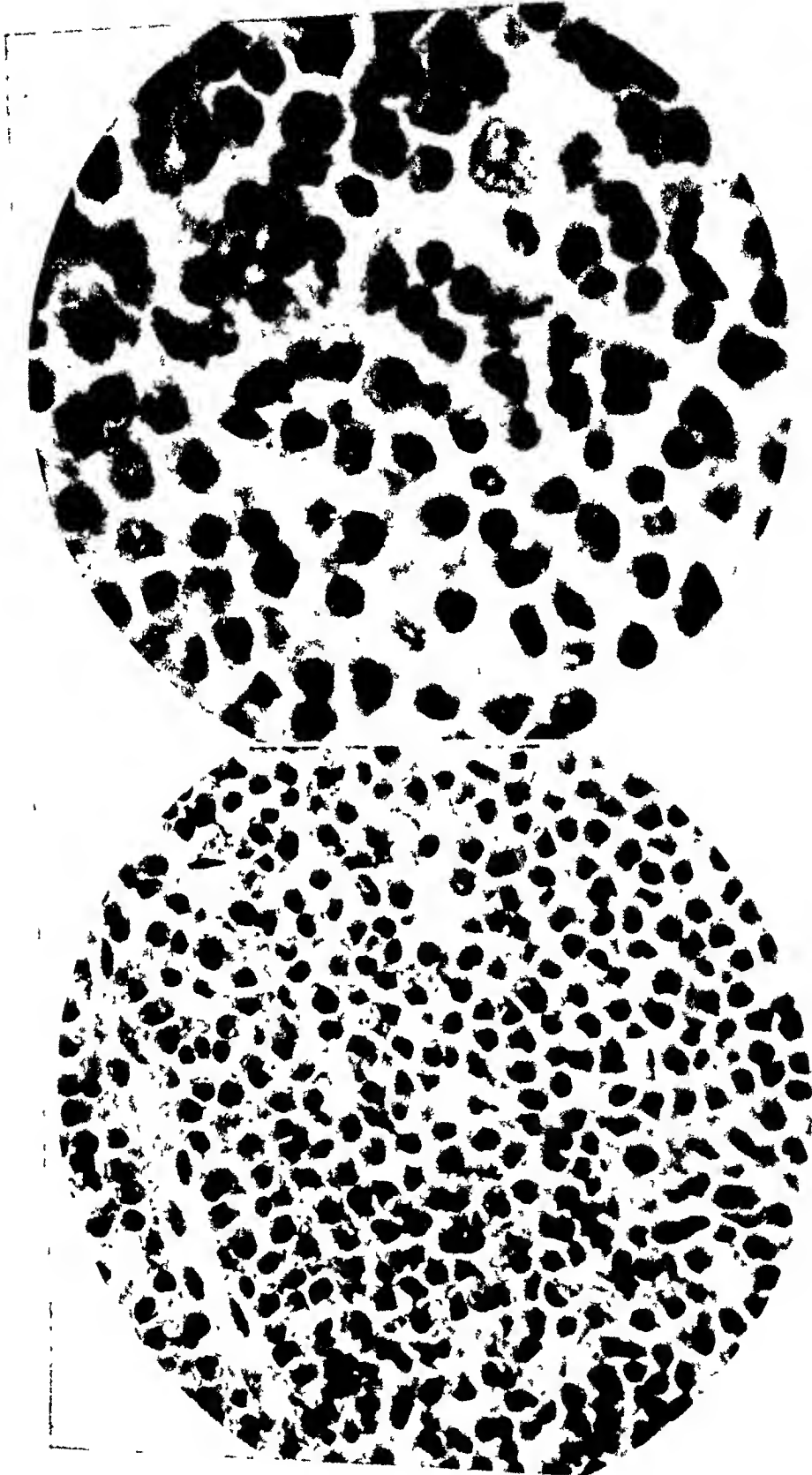


FIG. 4. Naffziger test showing incomplete spinal block.

Bence-Jones protein was found in the urine. The total serum protein level was 8.4 with albumin of 3.0 and globulin of 5.4.

Recovery following surgery was remarkable. Early pneumonic consolidation developed on the fifth day postoperatively, but was readily controlled by penicillin. A course of deep roentgen-ray irradiation was given using 200 KV with a 2 mm. cop-

* Pathological diagnosis made by Dr. Sylvester E. Gould, Pathologist for the Wayne County General Hospital and Infirmary.



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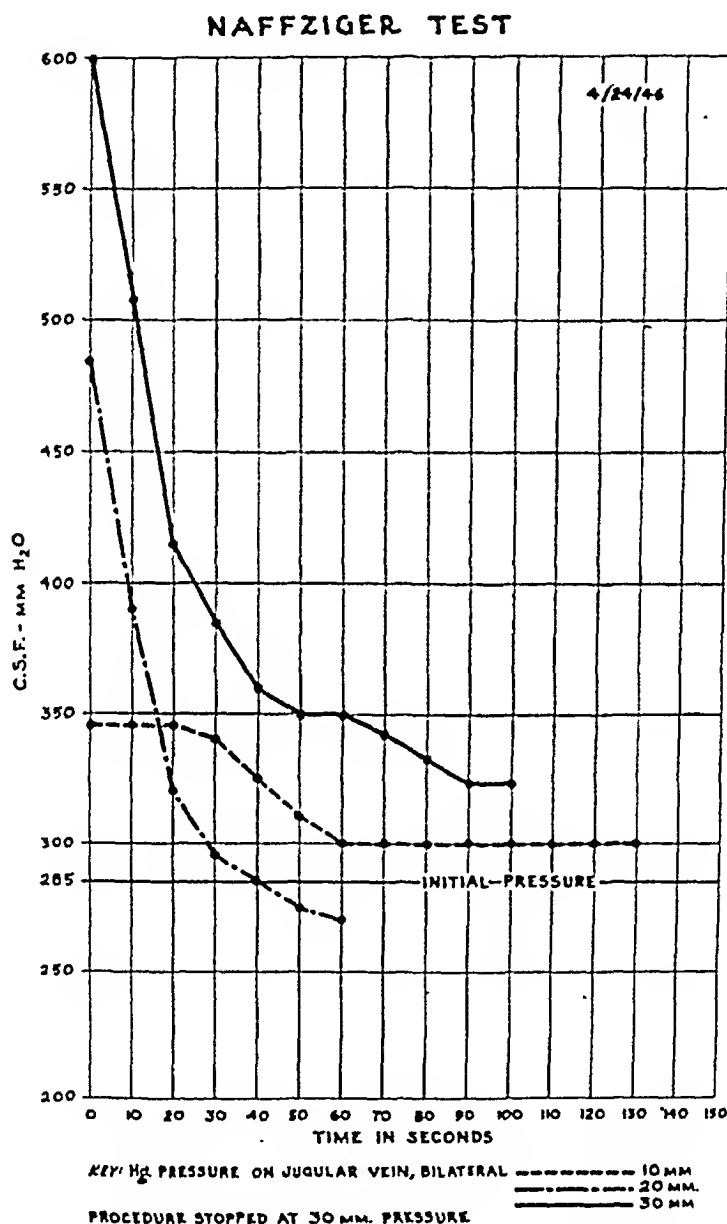


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FIG. 5. a. (Left) Photomicrograph of tumor mass. Magnification 550 \times .
 b. (Right) Photomicrograph of tumor mass. Magnification 1100 \times .

per-aluminum filter at a distance of 50 cm. delivering 15R per minute. Three ports were used: PA, AP right and AP left, on consecutive days for a total of 21 irradiations. Aside from anemia, the patient had no serious post-irradiation complications.

Following the laminectomy and irradiation the patient's return of muscular function and disappearance of associated neurological findings was spectacular. Within a week, he had definite increase in muscle strength; and in a month, he was walking



FIG. 6. Lateral x-ray view of skull showing punched out areas of multiple myeloma.

unaided. The patient was discharged May 20, and has been back at his factory job since that time. Examination on September 20 revealed an absolutely normal neurological picture. His serum protein level then was 12, his albumin being 2.0 and globulin 10.0. His only complaint was some slight numbness of the toes with exercise which was relieved by rest.

This case seemed worthy of presentation, not only to point out the necessity of considering multiple myeloma as an etiological agent in spinal cord compres-

sion, but also to emphasize the value of active therapy regardless of the ultimate prognosis in this type of case. Laminectomy plus roentgen-ray therapy has given in a majority of cases reported, relief of paraplegia and a return of the patient to economic and social sufficiency.

SUMMARY

A case of multiple myeloma with initial findings of cord compression has been presented. Laminectomy followed by roentgen irradiation has proved to be the most efficacious treatment in this and other reported cases. Active therapy should be offered to these patients in spite of the ultimately poor prognosis.

We are grateful to Mr. Albert Sadler for his photographic assistance in supplying our illustrations.

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A CASE OF INFECTIOUS MONONUCLEOSIS WITH ATYPICAL PNEUMONIA *

By MANUEL RODSTEIN, † M.D., *New York, N. Y.*

INTRODUCTION

ACCORDING to Smadel,¹⁶ "Primary atypical pneumonia is a clinical-pathological entity which has a diverse etiology. One of the first approaches to the problem of this disease should be the establishment of an etiological diagnosis wherever possible. In this way certain cases can be removed from the general group and studied in a more intelligent manner." Recent investigation of this disease includes the virus and bacteriological study of humans and animals, and the development of a number of serological tests for the detection of a widely different group of antibodies which develop chiefly during the convalescent phase of the disease. These include the cold agglutination reaction, the "indifferent streptococcus" agglutination test, the virus complement fixation tests and various reactions for syphilis and the heterophile antibody reaction.

We have recently had occasion to study a case which presents the characteristic hematological and serological picture of infectious mononucleosis with hepatic involvement and with clinical and roentgen-ray evidence of a pneumonitis

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† Assistant Resident in Medicine, Montefiore Hospital. From the Medical Service of Dr. Louis Leiter.

indistinguishable from that of the usual primary atypical pneumonia. An attempt has been made to establish the diagnosis of infectious mononucleosis as the etiological factor and the serological tests mentioned above have been performed in order to establish the relationship of the pulmonary findings with the systemic disease.

CASE REPORT

The patient was a white male, 21 years of age.

Past History: Essentially negative until April 4, 1946, when he was admitted to another institution with a two day history of fever, cough and substernal distress. Physical examination revealed dullness, increased breath sounds and a prolonged expiratory phase at the left base. Roentgen-ray revealed increased bronchial markings but no peri-bronchial infiltration. Sinus roentgenograms, taken because of



FIG. 1. Roentgenogram (September 3). Ill defined densities in lower portions of both lung fields.

severe frontal headache, were normal. Urine examination was normal, a Kahn test was negative and the white blood count was reported as 7300 with 74 per cent polymorphonuclears and 24 per cent lymphocytes. No abnormal forms were mentioned. The case was diagnosed as lobular pneumonia.

After discharge, there were no complaints until early May 1946, when he developed a stuffy nose, and after a cough of three days' duration and one day of fever,

chill and left chest pain, he was readmitted to the other institution on May 17, 1946 and remained there until May 31, 1946. A roentgenogram on May 17 showed increased broncho-vascular markings, peri-bronchial infiltrations over both lower lobes with foci of pneumonic infiltration, flattening of the left diaphragm and obliteration of the left costo-phrenic sinus. A diagnosis of primary atypical pneumonia was made. White blood count was 8000 with 72 per cent polymorphonuclears, 25 per cent lym-



FIG. 2. Roentgenogram (September 7). Increase in densities at both bases.

phocytes and 1 per cent monocytes and eosinophiles, without any mention of atypical forms. He was treated with penicillin and discharged in good condition.

Present Illness: In August 1946, he developed a cough productive of moderate amounts of yellowish sputum, followed in two and one half weeks by a stuffed-up feeling in the mid-chest. On the next day he developed nausea and weakness and dyspnea on exertion. On September 2, 1946, he was admitted to Montefiore Hospital with cough, fever and pain in the mid-chest on respiration. Physical examination revealed a thin, asthenic 21 year old white male, with a pulse rate of 108, respirations

of 30, blood pressure of 110 mm. Hg systolic and 68 mm. diastolic and temperature of 103.2° F. The only abnormalities detected were a small group of firm, discrete posterior cervical nodes on the right and an area of dullness, bronchial breathing and bronchial voice sounds in the right axilla. The left lung showed no abnormal signs.

Laboratory Findings: These are summarized for the most part in table 1. Additional findings include a normal urine on September 3; sputum on the same date showed *Staphylococcus aureus* predominating with a few non-hemolytic streptococci and a few colonies of pneumococci which did not type. Sputum of September 6 was negative for acid-fast bacilli on smear and on culture after two months. On

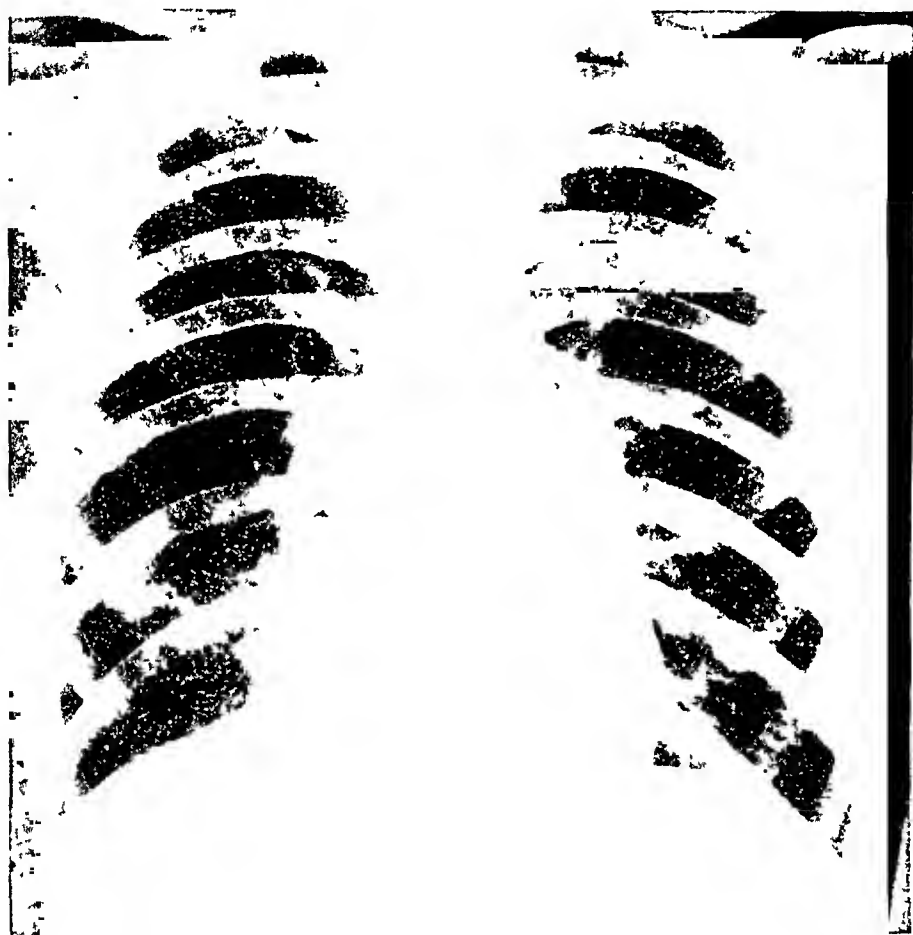


FIG. 3. Roentgenogram (September 18). Resolution almost complete on the left, partial on the right.

September 4 the blood sugar was 75 mg. per cent, the urea nitrogen 9.9 mg. per cent and the cholesterol 206 mg. per cent. The electrocardiogram on September 10 showed regular sinus rhythm. On September 23 the serum bilirubin was 0.1 mg. per cent and the urine was negative for bile and showed a faint trace of urobilinogen.

Course: Penicillin therapy was begun on the day of admission and continued through September 8, in dosages of 40,000 units every three hours intramuscularly. The temperature went on up to 105° on the second day, dropped to normal on the third day and spiked to about 100° on the fourth and fifth days and then remained normal. He was also given codeine for chest pain and a high vitamin, high calorie diet.

Throughout his stay, the spleen was never palpable, nor was there any additional adenopathy noted over that present on admission.

TABLE I

September..... Tests	3	4	5	6	9	11	13	16	17	18	23	30
Hemoglobin (grams)	12.5				12.0		12.5		6800			13.0
Erythrocytes (millions)	4.27				4.2		4.2		32			4.50
Leukocytes	10,300	5200	6200	7750	6400		6600		66		6400	6800
Polymorphonuclears (segmented)	62	45	27	15	43		33		7		6	64
Polymorphonuclears (band)	9	12	14	11	3		3		47		25	5
Lymphocytes (small)	13	24	29	63	50		49		5		0	0
Lymphocytes (atypical)	15	15	27	6	0		7		9		3	6
Monocytes	1	4	3	5	4		7					
Heterophile antibody titer		1:640			1:320	1:160		1:160		1:80	1:896	1:80
Cold agglutinin titer		1:1			1:10	1:80		1:80				1:10
Davidsohn test-heterophile antibody titer*												
A. Non-absorbed												
B. Absorbed with												
1.-Guinea pig kidney												
2.-Boiled beef erythrocytes												
Cephalin flocculation												
Thymol turbidity												
Streptococcus MG**												
Complement fixation***												
Psittacosis antigen												
Kahn negative												
Wassermann negative												
Typhoid O and H												
Paratyphoid A and B												
Brucella												
Proteus OX 19												
										3 plus 16	1:448	
										Negative	1:No agglutination 3 plus 13	
										Negative		Negative
										Negative		Negative
										Negative		Negative

* By Dr. Annis E. Thomson, Research Laboratories of the New York City Board of Health.

** By Dr. Harold S. Ginsberg, Hospital of the Rockefeller Institute for Medical Research.

*** By Dr. Karl F. Meyer, George Williams Hooper Foundation, San Francisco, California.

On September 3, the signs at the right axilla were unchanged and dullness with diminished breath sounds and a few crepitant râles were noted at the left base posteriorly. A roentgenogram showed poorly circumscribed patches of density scattered throughout the lower portions of both lung fields, suggesting the bronchlobular and bronchopneumonic involvement of primary atypical pneumonia (figure 1).

On September 7, roentgen-ray (figure 2) showed a diffuse increase in density over the lower portion of the right lung and the left lung. A roentgenogram on September 12 revealed a decrease in the densities. During this period diffuse moist

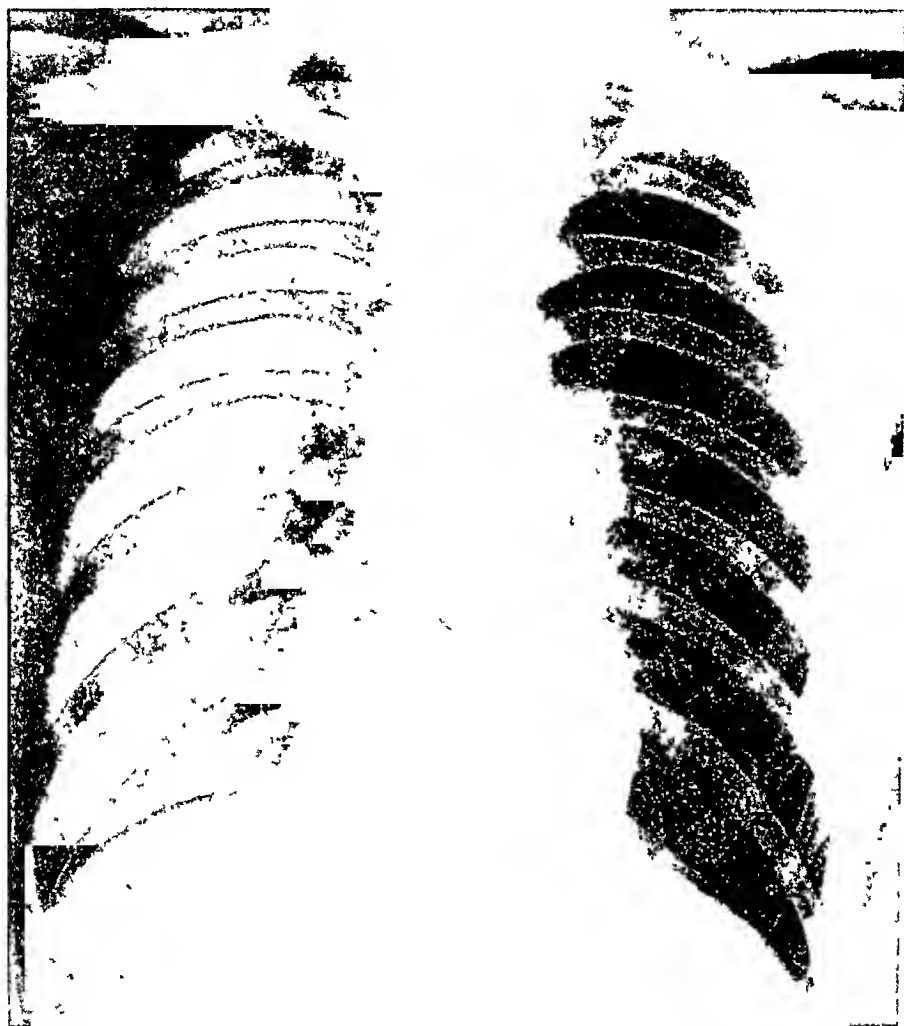


FIG. 4. Roentgenogram (September 30). Resolution complete except for exaggeration of truncal markings at the bases.

râles over the right lung base developed and persisted along with signs of consolidation over this area. By September 15 the signs began to diminish bilaterally and the lungs were clear to auscultation by September 20. A roentgenogram on September 18 (figure 3) revealed almost complete resolution of the process on the left and partial resolution on the right. On September 30 (figure 4) only exaggeration of the truncal markings at both bases pericardially was noted, which was considered a residue of the pneumonic process.

The presence of atypical lymphocytes and a mononucleosis after an initial normal percentage of polymorphonuclears from September 3 to September 23, when the white blood count became completely normal, is shown in table 1.

CASE REPORTS

In view of those findings heterophile antibody and cold agglutinin titers were performed at repeated intervals and the results are shown in table 1.

To serve as a confirmatory test for the specificity of the heterophile antibody test a special modification of the Davidsohn test was performed for us by Dr. Annis E. Thomson, the results of which are shown in table 1. They were interpreted by her as "Serologically positive for infectious mononucleosis in high titer."

The results of tests for agglutinins for *Streptococcus MG* are also shown in table 1 (performed by Dr. Harold S. Ginsberg).

Dr. Karl F. Meyer found serum of September 17 negative for complement fixation with psittacosis antigen.

DISCUSSION

The preceding history in this case is that of successive attacks of what was diagnosed at another institution as lobular pneumonia and primary atypical pneumonia with normal blood counts and smears. On the present admission the only significant findings are confined to the lungs and are indistinguishable from those present in primary atypical pneumonia. Smear and culture of the sputum did not reveal any pathogens. The few pneumococci were not typable. The roentgenograms were interpreted as showing the bronchlobular and bronchopneumonic involvement characteristic of primary atypical pneumonia. The apparent response to penicillin therapy has not been described as being characteristic of infectious mononucleosis or primary atypical pneumonia, and cannot be ascribed to the organisms in the sputum.

An analysis of the results of the battery of tests considered of diagnostic significance in primary atypical pneumonia shows that the patient developed a significant titer of cold agglutinins, 1/80, at about the beginning of the third week of his illness, and returned to normal by the fifth week. This corresponds to the course of these agglutinins as described by Finland⁸ in primary atypical pneumonia. Various authors have found significant titers of cold agglutinins present in the course of primary atypical pneumonia, in from approximately 30 to 70 per cent of their series; Finland et al.⁸ 68.5 per cent, Favour⁹ in 32 out of 46 cases, Horstman and Tatlock¹¹ 27 out of 40 cases, McNeil¹² 15 out of 15 cases, The Commission on Acute Respiratory Diseases¹⁸ 30 out of 93 cases, Turner²⁰ 44 out of 83 cases, and Florman¹⁰ 63 per cent of 68 cases. However, its differential diagnostic value in this case is impaired by the fact that significant titers of cold agglutinins have been found in infectious mononucleosis by several authors, i.e. Spingarn et al.¹⁷ who found titers of up to 1/896 in five cases of infectious mononucleosis, all with high titers of heterophile antibodies and by McNeil¹³ who found a significant titer in one out of five cases of infectious mononucleosis.

The test for agglutinins for the *Streptococcus MG*, on sera taken during the acute and convalescent phases of the illness was negative as performed through the courtesy of Dr. Harold S. Ginsberg of the Rockefeller Institute. Curnen et al.⁴ found this test positive in significant titers in 68 of 106 cases of primary atypical pneumonia; Finland et al.⁷ found significant results in about half of 78 cases, and Florman¹⁰ in 17 of 36 cases. Both Florman and Curnen found that the majority of cases with positive tests appeared in individuals who had developed positive cold agglutination reactions.

Serum was negative for complement fixation with psittacosis antigen when tested by Dr. Karl E. Meyer¹⁴ who found positive results with this test, accord-

ing to his criteria, in 10 out of 45 cases of primary atypical pneumonia, Florman⁹ using "lygranum CF" antigen found 28.4 per cent of 102 primary atypical pneumonia cases yielding positive results. In another series the same author obtained 26 per cent positive out of 35 cases¹⁰. In both methods only the appearance of, or a rise of antibody titers during convalescence is considered significant. Most of Florman's positives appeared in cases without a significant cold agglutinin titer.

Increased heterophile antibody titers have been reported in primary atypical pneumonia by Wechsler et al.²¹ with three cases in which titers rose from 1/28 to 1/224, 1/112 to 1/224, and stationary at 1/112 during the course of the disease. However, abnormal lymphocytes could not be demonstrated on repeated examinations, a mononucleosis never developed and the Davidsohn absorption test was negative in the two of such cases in which it was done. Florman¹⁰ in 73 consecutive sera from cases of primary atypical pneumonia found heterophile antibody titers of 1/40 in only two cases. Young²² in a series of 15 primary atypical pneumonias found only two that developed significant titers of heterophile antibodies, 1/64 and 1/512, both of which developed during convalescence, the sera having been negative in the acute phase of the disease. Adams¹ in an epidemic of primary atypical pneumonia among the British troops in the Naples area in 1945, found 36 per cent (18) of their cases had heterophile antibody titers of over 1/448. Ten of these had a preceding history of malaria. No mention is made of the use of Davidsohn confirmatory tests.

The data that tend towards a diagnosis of infectious mononucleosis in this case are: (1) The characteristic hematological picture; (2) the positive Davidsohn reaction with the positive heterophile antibody titers; (3) the evidence of hepatic involvement; (4) the fact that Wechsler et al.²¹ have reported a group of cases in which "a pneumonitis closely resembling atypical pneumonia, can occasionally be due to the unknown etiologic agent of infectious mononucleosis"; (5) that Ziegler²³ has described a case of infectious mononucleosis which at post mortem showed in the lungs a distinctive pathologic process attributable to the disease.

1. The characteristic hematological picture consisted of the presence in the blood of "leukocytoid" lymphocytes in the percentages shown in table 1, without a preceding upper respiratory infection or allergic state¹⁵, and of the absence of infectious hepatitis² in which states they are represented as being common. Young²² in 15 cases of primary atypical pneumonia found 11 with 10 to 25 per cent monocytes on admission and one case with 25 per cent monocytes in the convalescent period, but makes no mention of atypical forms.

The initial leukocytosis is in accord with the findings of Wechsler et al.²¹ The mononucleosis present after the initial leukocytosis was considered an essential sign of the disease by Bernstein.³

2. The repeatedly positive heterophile antibody titers and the positive confirmatory Davidsohn reaction are in favor of the presence of infectious mononucleosis. The positive Davidsohn test as performed by Dr. Annis E. Thomson using her special modification of the original technic tends to rule out the possibility of the elevated heterophile antibody titer being due to normally present Forssman antibodies or those produced in serum sickness. As to the reliability of this test, Kaufman¹² using the above technic, found in 78 cases of infectious mononucleosis 12 negative and 66 positives. In 10 of the negatives

both antigens were completely absorbed and in one of these the test later became positive. Demanche⁵ in 57 cases, found 55 positive and one case with no absorption by either antigen and another had absorption with beef red blood cells only after 24 hours. Wechsler et al.²¹ found the test strikingly confirmatory in many cases but not uniformly satisfactory, as in some cases both antigens failed to completely absorb the agglutinins and in some of these the beef red blood cells absorbed a smaller percentage of the agglutinins than did the guinea pig suspensions. In other cases both antigens completely absorbed the agglutinins without a former history of serum sickness or liver infection being present. These discrepancies may be explained by some evidence that in infectious mononucleosis there may be an early rise in Forssman antibodies, before those typical of infectious mononucleosis increase.

3. The evidence for hepatic involvement as shown by the repeatedly positive cephalin flocculation and thymol turbidity tests can be ascribed to infectious mononucleosis, as increased heterophile antibody titers have not been reported in infectious hepatitis.²

4. Wechsler et al.²¹ in 14 out of 556 cases of an epidemic of infectious mononucleosis at an army post, found roentgen-ray evidence of a pneumonitis. The appearance of the lesions was indistinguishable from those described in primary atypical pneumonia and the findings cleared very rapidly, a phenomenon which they report as occasionally occurring in primary atypical pneumonia. The sputa in all of their cases, as in ours, did not contain any significant pathogenic organisms and the blood cultures were negative. However, some type of sore throat was present in all of their cases and there was none in our case.

They also noted in their cases similarities to primary atypical pneumonia in the character of the cough, the asthmatic wheezing, the disparity between the physical signs and the extent of the pulmonary involvement and the failure to respond to sulfadiazine.

5. Ziegler²³ in the lungs of a case of infectious mononucleosis at necropsy found lesions in which there was distention and often obstruction of the alveolar capillaries with characteristic mononuclear cells, together with scattered perivascular and interstitial mononuclear infiltrates. There were more of these peculiar leukocytes in the capillaries than erythrocytes and they were the same types as were present in other organs. The bronchial walls were moderately infiltrated by mononuclear cells and the lining epithelium was greatly swollen but not significantly exfoliated. In this case there was a hepatitis, nephritis and splenitis of a characteristic and peculiar type in addition to the pneumonitis, and as certain other organs were not involved, i.e. heart and appendix, he felt that this fact, together with their morphologic characteristics, suggested strongly that they represent the reaction of the tissues to foci of infection and that they are not merely a mechanical overflow of mononuclear leukocytes from the blood stream.

In this case, the Wassermann and Kahn reactions were negative although many false positives have been noted in both diseases.

The agglutination reactions for typhoid, paratyphoid, proteus OX 19, and brucella were also negative. They have been reported as elevated sometimes in infectious mononucleosis by Wechsler et al.,²¹ and elevated in some cases of primary atypical pneumonia by Chesney and Gardner (quoted by ⁹).

SUMMARY

A case has been presented in which the symptoms, physical signs and clinical course are similar to those of primary atypical pneumonia. Roentgen-rays of the lungs revealed progressive changes through to almost complete resolution and are interpreted as being characteristic of the same disease. A significantly elevated cold agglutinin titer was present but agglutinins for *Streptococcus MG* and psittacosis were not present.

On the other hand, the characteristic hematological picture of infectious mononucleosis was present with atypical lymphocytes, an initial leukocytosis followed by a mononucleosis and a return to a normal blood picture. The heterophile antibody titers were consistently elevated declining from an initial peak, and the Davidsohn test was interpreted as being serologically positive for infectious mononucleosis in a high titer. The cephalin flocculation and thymol turbidity tests were strongly positive on two occasions.

It is suggested that in the presence of the hematological and serological picture of infectious mononucleosis, the pneumonitis present represents a manifestation of the infection by the unknown etiologic agent of infectious mononucleosis.

The writer wishes to extend his appreciation to the following: Miss Ruth Stein for her invaluable technical assistance in the hematological work-up of the case; to Dr. Louis Leiter for his helpful criticism; to Drs. Harold S. Ginsberg, Annis E. Thomson and Karl F. Meyer for the performance of special serological tests.

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Q FEVER: CASE TREATED WITH STREPTOMYCIN *

By LEON ROSEVE, M.D., *Santa Monica*, HAROLD E. WEST, M.D., *Los Angeles*
and ALBERT G. BOWER, M.D., F.A.C.P., *Pasadena, California*

Q FEVER was described first as a severe influenza-like disease in Queensland, Australia in 1937, where it affected bushmen, abattoir and dairy workers. Evidence from Australia indicates that the tick (*Haemaphysalis humorosa*) and the bandicoot (*Isodon torosus*) constitute important vectors and a host reservoir. Although ticks infected with *Rickettsia burneti*, the cause of Q fever, have been collected from several northwestern and southwestern states,¹ only a few naturally occurring infections have been reported from this country. It now appears that Q fever is more widespread than originally thought.

Outbreaks of Q fever were reported during the latter part of World War II occurring among troops in the Mediterranean area^{2,3} and in Panama.⁴ In June 1945, an outbreak of atypical pneumonia occurred in the 717th Bomb Squadron, which had just returned to the United States from Italy. During a period of two weeks, 145 (38 per cent) of the 379 officers and men of the Squadron were hospitalized at Camp Patrick Henry, Virginia,⁵ where the diagnosis of Q fever was established.

Several outbreaks of Q fever have been reported by the National Institute of Health^{6,7} where the disease is being studied. The first sizable outbreak of

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From the University of Southern California School of Medicine and the Communicable Disease Unit of the Los Angeles County General Hospital.

Q fever acquired naturally in the United States occurred among stockyard and slaughterhouse workers in Amarillo, Texas, during March 1946.^{8, 9, 10, 11} There were 55 cases and two deaths among 136 exposed persons, an attack rate of 40 per cent. The clinical and roentgenographic features of 18 hospitalized patients studied were similar to those described in the Mediterranean outbreak and among infected laboratory workers. An outbreak of Q fever has recently occurred in one of the Chicago packing plants, but the details of this outbreak have not yet been published.¹² These two naturally occurring outbreaks, in Amarillo and Chicago, were probably acquired by inhalation of tick feces or other rickettsial contaminated material, both outbreaks occurring in slaughterhouses with no evidence of man to man transfer.

Q fever was identified in the Artesia area in Los Angeles County in May 1947.¹³ More than 100 cases have been reported to date from this region which covers an area approximately 50 miles wide. In May 1947, the United States Public Health Service sent Dr. C. C. Shepard to Southern California to investi-



FIG. 1. Showing a left lower lobe pneumonia accompanied by pleuritis.

CASE REPORTS

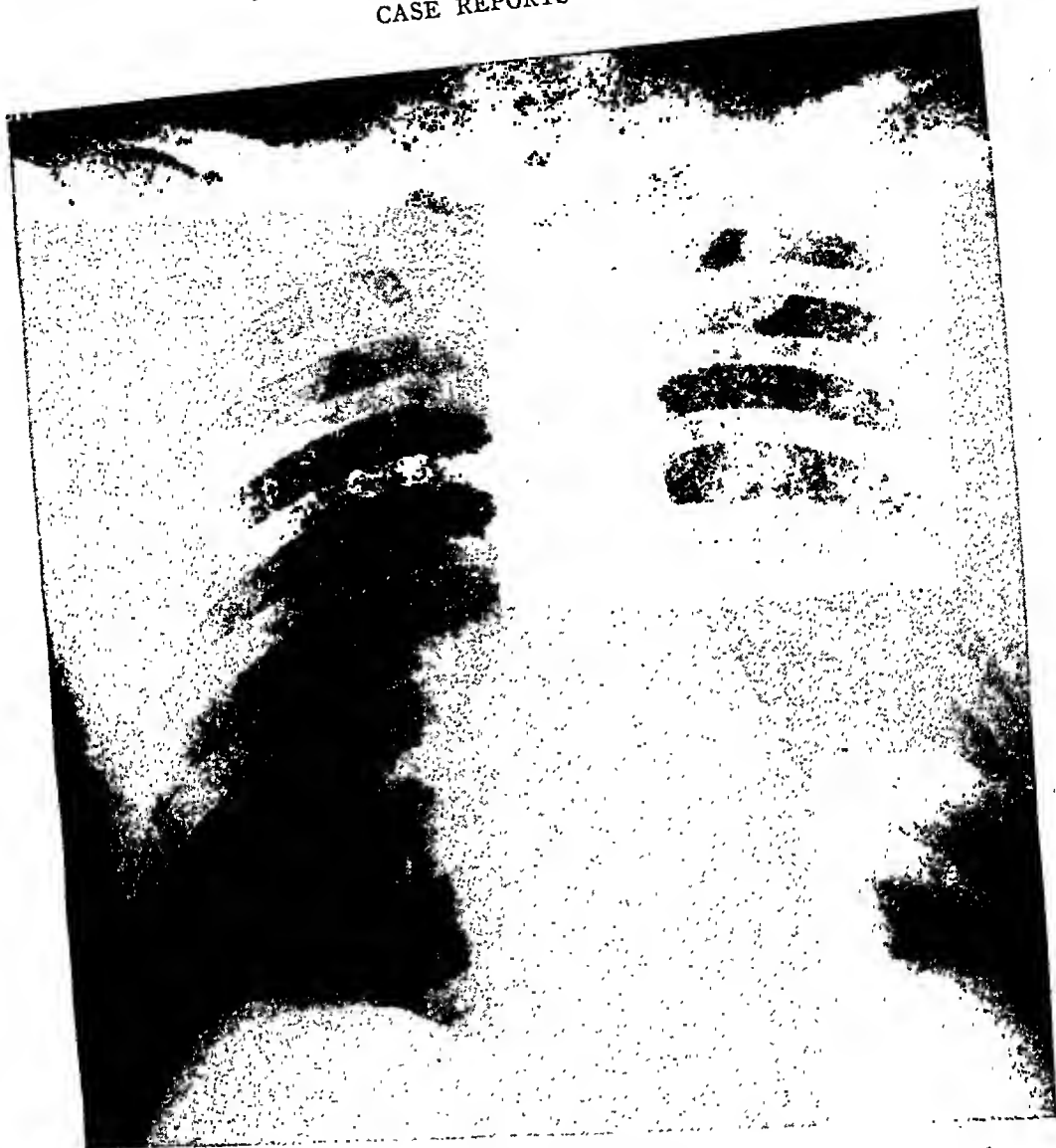


FIG. 2. Showing slight infiltration in the right perihilar and basilar areas but otherwise unchanged.

gate this outbreak, the details of which are still unpublished. The following case was referred by him to the Communicable Disease Unit of the Los Angeles County Hospital, with diagnosis of Q fever.

CASE REPORT

T. T. Q., a 39 year old male derrick rigger, living in Artesia, Los Angeles County, was well until May 18, 1947. At that time he was bitten on the left elbow by a tick, with subsequent itching and pain at the site of the bite. The illness began insidiously on May 21. He complained of generalized arthralgia and myalgia. Fever developed the next day and he was confined to bed. On May 23 the temperature was 101° F. to 102° F., and he had a severe headache and pain in the left chest accompanied by a slight cough. On May 24 fever was 104° F. and he was sent to a private hospital with the diagnosis of lobar pneumonia. He was given sulfadiazine and 100,000 units of penicillin every four hours for four days with no effect, following which he was transferred to the Communicable Disease Unit of the Los Angeles County Hospital on May 28, with the diagnosis of Q fever made by Dr. Shepard.

Physical examination revealed a well developed, thin, white male, acutely ill, toxic, dehydrated, perspiring profusely, completely disoriented and irrational, and with variable periods of violent mania or lethargy. There was a persistent cough, slightly productive, with occasionally blood tinged sputum. The fever was 104° F., the pulse 100, the respirations 28, and the blood pressure 132 mm. Hg systolic and 88 diastolic. There was mild nuchal stiffness and a bilateral positive Kernig sign. A diffuse, red, macular rash was present over the upper one-third of the anterior chest. No adeno-

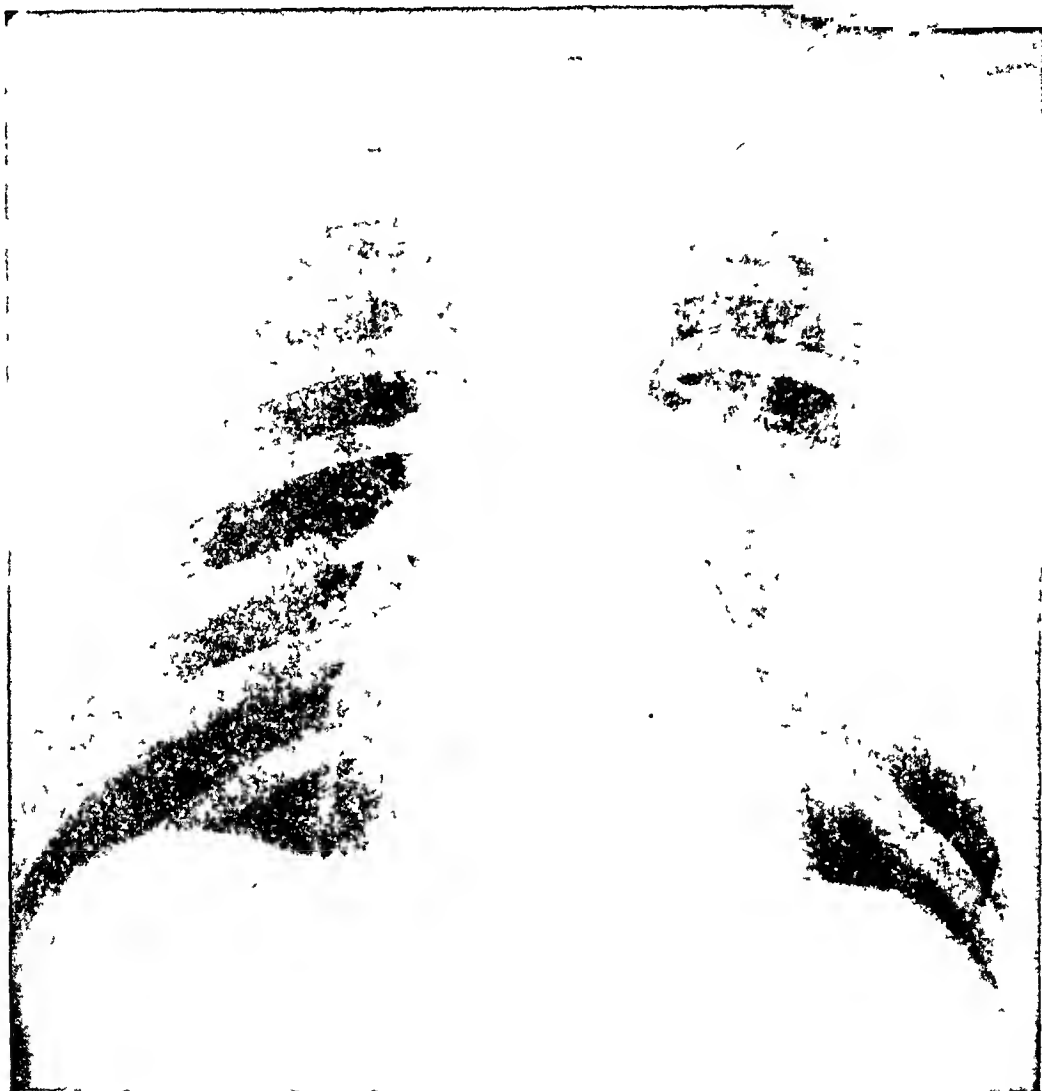


FIG. 3. Showing partial resolution.

pathy was noted. Mild bilateral conjunctivitis was present. Examination of the chest revealed slight limitation of expansion on the left side with dullness, decreased breath sounds, and frequent râles in the left mid posterior lung field, interpreted as consolidation with slight pleural effusion. The right lung was normal. The spleen was not enlarged. The remainder of the physical examination revealed no abnormalities.

Roentgen-ray examination of the chest on May 28 (figure 1) revealed a left lower lobe pneumonia accompanied by pleuritis. The heart and aorta were normal. On June 2 (figure 2) there was slight infiltration in the right perihilar and basilar areas

but otherwise unchanged. On June 9 (figure 3) partial resolution of the infiltration in the left lung was demonstrated with persistent infiltration in the mid lung.

Urinalyses were negative. A blood count on admission revealed hemoglobin 16.5 grams, white cell count 8500 with 90 per cent neutrophils. On June 2 the hemoglobin was 14 grams and white cell count 7500. On June 4 the white cell count was 5200 with 70 per cent neutrophils. On June 6 the hemoglobin was 11 grams and white cell count 7350. The Wassermann test was negative. Blood cultures taken May 29, May 30 and June 2 were negative. Urine and stool cultures were negative. Spinal fluid examined on May 28 was normal. Agglutinations with *Proteus* OX-19 were negative. Streptomycin blood levels taken May 30 were less than 40 micrograms per ml. and more than 25, and on June 2 the level was 25 micrograms per ml. Complement-fixation tests for Q fever were done by the United States Public Health Service at Bethesda, Maryland. The results were reported as follows: May 28, negative; June 2, positive 1:128 (end point not reached); June 9, positive 1:128 (end point not reached).

His course during the first 48 hours in hospital was acute. He was extremely irritable, irrational and perspired profusely. The cough gradually subsided and the rash faded within 48 hours. He was given supportive therapy, oxygen by nasal catheter, intravenous fluids and food by Levine tube. Streptomycin was started May 29 with the following dosage: 3 grams in divided doses every three hours daily for four days, then 1.5 grams for four days. The patient's temperature, which had been between 102° F. and 104° F. for five days, started to fall after 48 hours of streptomycin therapy, becoming normal for the first time four days after this treatment was started, and except for one rise to 100° F. the patient remained afebrile. He was discharged after 12 days in the Los Angeles County Hospital, asymptomatic and in good general condition.

COMMENT

There are no human cases of Q fever reported in the literature that have been treated with streptomycin or para-aminobenzoic acid. It has been found at the United States Public Health Laboratory at Bethesda, Maryland, that streptomycin is effective in Q fever in laboratory animals.¹⁴ It was for this reason that streptomycin was used as a choice of treatment.

Prior to admission to the hospital, sulfadiazine and penicillin employed in combination did not alter the patient's course. Streptomycin was started in this case on the patient's ninth day of illness and clinical improvement was noted in 48 hours with progressive defervescence of fever during the 96 hours following the beginning of therapy. It is difficult to say with certainty that improvement would not have occurred without streptomycin. In the series of cases reported in the Amarillo outbreak, 11 of 18 hospitalized patients had normal temperatures on the twelfth day of illness without specific therapy. It is felt, however, in view of the severity of his infection and extent of pulmonary involvement, that clinical improvement may well be attributed to streptomycin. Further clinical trial with streptomycin early in the course of Q fever is necessary for adequate evaluation.

SUMMARY

Q fever has recently been identified in the Artesia area of Los Angeles County. A case of Q fever is reported here with clinical and roentgenographic findings consistent with this diagnosis and confirmed by positive complement-fixation tests. Treatment with streptomycin was instituted and proved satis-

factory, although further clinical investigation is necessary to establish its efficacy in this disease.

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EDITORIAL

THE MECHANISM OF THE CRISES IN FAMILIAL HEMOLYTIC JAUNDICE

SINCE the early publications of Chauffard it has been well known that patients with this disease are prone to suffer acute exacerbations which are commonly termed hemolytic crises—"crises de déglobulization." During such periods there is usually fever, malaise, prostration, shortness of breath, and often acute abdominal pain with anorexia and vomiting. There is a rapid increase in the anemia, so that the red cell count and hemoglobin are often reduced to half of the original figures within a week or less. In occasional cases this may progress to a fatal termination, but as a rule after one to two weeks there is an arrest of the process with relief of the symptoms and a gradual, sometimes rapid, return of the red cells and hemoglobin to their former values.

It has been commonly assumed that such crises are due to an abrupt increase in the activity of the hemolytic process which is believed to characterize the course of the disease. Many observers have reported an increase in the number of spherocytic red cells and in their fragility in hypotonic salt solution. It has been generally stated that there is an increase in the depth of the jaundice, in the bilirubin in the serum, in the urobilinogen in the urine, in the size of the spleen, and in other indications of increased hemolysis.

This commonly accepted view has recently been questioned by Owren¹ who has reported careful studies of six patients observed through such a crisis with serial observations of the blood and punctates of the sternal bone marrow. The clinical symptoms in most respects were quite like those usually described; there was an abrupt onset with fever lasting about ten days and returning to normal as hematological improvement began. The spleen did not increase demonstrably in size, however, and in all cases the jaundice decreased in intensity during the crisis.

There was, as usual, a rapid fall in red cell count and hemoglobin to about half the original figures by the sixth day. With this there was a fall in the total leukocyte count, in the percentage of granulocytes and in the platelet count. The reticulocytes practically disappeared from both the peripheral blood and the sternal marrow (punctate). The most surprising observation, however, was the fall (during the crisis) of the serum bilirubin and icterus index to normal figures and a diminution of the urobilinogen excreted in the urine. These facts, Owren believes, indicate that hemolysis is not increased during the crisis, but on the other hand it is actually diminished, probably because the total volume of red cells actually removed from the circulation and destroyed daily is progressively reduced as the anemia increases in severity.

¹ OWREN, P. A.: Congenital hemolytic jaundice. The pathogenesis of the "hemolytic crises," *Blood*, 1948, iii, 231-248.

The termination of the crisis was marked first by a neutrophilic leukocytosis with a shift to the left in the granulocytes; next by an increase in platelets; and then, about 10 to 14 days after the beginning of the crisis, there was an abrupt, critical rise in reticulocytes (to about 20 to 30 per cent), followed by a more gradual return of the red cell count and hemoglobin to their former levels. He attributes the conflicting reports in the literature regarding these cytological changes to differences in the stage of the cycle at which examinations were made. Often patients are not seen until the crisis is over, and the reported counts were made during the recovery phase.

The bone marrow in this disease usually shows a hyperplastic, normoblastic type of marrow in which the proportion of erythroblastic cells is increased so that they constitute 40 to 60 per cent or more of the marrow cells instead of the normal 15 to 30 per cent. Films obtained during the crisis in these patients showed an extreme reduction in the erythroblastic cells, which were represented only by a few normoblasts and a few cells of primitive type (erythrogonos). In one case the number was reduced from 53 per cent eight days before the crisis to 4.8 per cent on the fourth day of the crisis and 4.2 per cent on the sixth day. With termination of the crisis there was an extraordinary regeneration and proliferation of these cells which, in the case mentioned, constituted 29 per cent of all the marrow cells on the ninth day after the onset of the crisis and 81 per cent on the twelfth day. Photomicrographs taken during this period illustrate the successive development from the primitive erythrogonos of pronormoblasts, basophilic normoblasts, polychromatophilic and orthochromatic normoblasts.

On the basis of these observations Owren believes that the crises are not caused by an increased hemolysis of red cells but by an abrupt, severe, but transient aplasia of the marrow. He would therefore call them aplastic, not hemolytic, crises.

To devise a reasonable explanation of the crises it is necessary to consider the factors which cause the abnormalities present during the long remissions between the crises. Concerning this there is no general agreement. There is no doubt that increased hemolysis is a fundamental and constant feature of the disease. The majority of hematologists, however, have accepted more or less completely the view which was vigorously supported by Naegeli that the fundamental fault is in the bone marrow. This results in the production of defective red cells which are rapidly removed from the circulation, and this removal is explained by the normal activities of the usual physiological mechanisms for the removal of worn out red cells without assuming the presence of an abnormal hemolytic agent. The spherocytosis with the closely parallel increase in fragility would be one objective manifestation of the defect.

That spherocytosis and increased fragility are not pathognomonic of familial hemolytic jaundice has been amply demonstrated, particularly by

Dameshek and associates.² Spherocytes may be present in a variety of severe hemolytic anemias which are otherwise entirely unrelated to familial hemolytic jaundice. There is much evidence, also, that the immature erythrocytes in familial hemolytic jaundice are normal in shape and that the spherocytosis appears only after maturation and discharge of the cells into the circulation, where they may quickly suffer injury. This injury, however, might arise from physical forces or chemical substances which would not affect normal red cells, and not necessarily from some abnormal hemolytic agent.

Evidence tending to support this view has been obtained from experimental transfusions. It has been shown, e.g., by Dacie and Mollison,³ using a modification of Ashby's technic, and confirmed by Owren,¹ that when cells from patients with familial hemolytic jaundice are transfused into normal individuals, they are removed with great rapidity, usually all within two weeks. This is not surprising, since such cells presumably may have been injured while still in the circulation of the donor, before the transfusion. When, however, patients with familial hemolytic jaundice are transfused with normal blood, the cells remain in the circulation as long (about 100 to 120 days) as they do in normal individuals. On the other hand, when patients with severe hemolytic anemia of other types were transfused with normal blood, the cells were eliminated rapidly, usually within 20 days.³ Such observations suggest that conditions in familial hemolytic jaundice are different from those in most other hemolytic anemias and do not support the assumption of an abnormal hemolytic agent unless it be one whose activity is restricted to the individual's own cells. There is no direct proof of such an agent except Dameshek's observation⁴ of autohemolysins in the serum of occasional individuals during crises. This observation is important if confirmed, but the technical difficulties in hemolytic experiments with defective and damaged red cells are very great. Without definite proof, it seems more logical to accept the hypothesis of an inherent cellular defect rather than to assume the existence of a hemolytic agent of such extraordinary specificity.

A major difficulty in accepting Owren's view that the crises are "aplastic" is the rapidity with which a profound degree of anemia develops. Owren attempts to meet this by demonstrating the short life span of the red cells in these patients, less than 14 days. Half of the red cells might, therefore, be removed within six or seven days without assuming an increased rate of hemolysis. The crises in the cases he reported, including one followed throughout a cycle, might be accounted for on this basis. Many fulminant cases have been reported by other observers, however, in which equally severe anemia has apparently developed within two or three days. Patients

² DAMESHEK, W., and SCHWARTZ, S. O.: Acute hemolytic anemia (acquired hemolytic icterus, acute type), *Medicine*, 1940, xix, 231-327.

³ DACIE, J. V., and MOLLISON, P. L.: Survival of normal erythrocytes after transfusion to patients with familial hemolytic anemia, *Lancet*, 1943, i, 550-552.

⁴ DAMESHEK, W.: The hemolytic crisis, *Blood*, 1948, iii, 307-308 (Editorial).

are rarely observed, however, until the crisis is well under way, and it is possible that a substantial increase in anemia occurs before the appearance of clinical symptoms which are regarded as marking the onset of the crisis. It is also conceivable, although there is no proof whatsoever, that the cells formed shortly before the crisis while aplasia of the marrow is developing might be more vulnerable than usual. These points can be determined only by intensive study of patients before and throughout the crises.

That extrinsic factors are probably concerned in precipitating the crises is indicated by their occasional occurrence in rapid succession in several members of the same family (e.g., Scott,⁵ Dameshek,⁶ Owren¹). An infectious agent has been suggested, but in no instance has it been possible to demonstrate what these factors are or how they operate.

Owren's observations of pancytopenia and disappearance of reticulocytes during the crises are in harmony with those of several others, e.g., Scott,⁵ and Dameshek,^{4, 6} who has also confirmed the aplasia of the erythropoietic tissue in the marrow.⁴ Regardless of the rôle which increased hemolytic activity may play, there is strong evidence that a virtual cessation of red cell production occurs during the crises. The beneficial effect of splenectomy suggests that this organ has exerted an inhibitory effect on the marrow and that the crises may be in part, at least, another manifestation of "hypersplenism," which has been shown to be the cause of a number of other hematological disturbances.⁷

P. W. C.

⁵ SCOTT, A. M.: The serial onset of acute blood crises in an entire family, *Lancet*, 1935, ii, 872-874.

⁶ DAMESHEK, W.: Familial hemolytic crisis. Report of three cases occurring within ten days, *New England Jr. Med.*, 1941, cciv, 52-56.

⁷ Editorial (M.S.S.): The concept of hypersplenism, *Ann. Int. Med.*, 1946, xxv, 868-870.

REVIEWS

Treatment of Bronchial Asthma. By VINCENT K. DERBES, Instructor in Medicine and Preventative Medicine, Tulane University of Louisiana, School of Medicine, and HUGO T. ENGELHARDT, M.D., F.A.C.P., Instructor in Clinical Medicine, Baylor University College of Medicine, Houston, Texas; and a group of seventeen collaborating contributors. 466 pages; 24 × 16 cm., with 61 illustrations. The J. B. Lippincott Company, Philadelphia, London, Montreal. 1946. Price, \$8.00.

This volume consists of two parts: Orientation and Clinical Aspects. There is a total of 23 chapters. The contributors are authors whose names are well known in the literature of their respective specialties.

In Part One, consideration is given first to the history of bronchial asthma and then to definitions and classification, statistics, causative factors, anatomy, physiology and to the immunologic mechanisms of asthma.

In Part Two, clinical phases are discussed. The disease is described and methods of testing discussed. The house-dust factor is considered at length and with profit. Etiological groups are considered as such, namely, foods, pollens and spores, psychogenic factors and so forth. A chapter on diagnosis is given and there are several chapters on treatment. Finally, complications and cardiac asthma are discussed.

The chapters by Milton Cohen on immunology; Bernard G. Efron on the house-dust factor; Oren C. Durham on pollen and fungus-spore factors; Alton Ochsner on surgical considerations; and Paul White on cardiac asthma, are particularly satisfactory.

The book exhibits the somewhat uneven presentation of material and the minor contradictions that seem inevitable in volumes with multiple authors. To the experienced allergist this means little, but, to the general practitioner, it may well be confusing. The general excellence of the presentation compensates, however, for any points of weakness.

H. M. B.

War Neuroses. By ROY R. GRINKER, Lt. Col., M.C., and JOHN P. SPIEGEL, Major, M.C., A.A.F. 145 pages; 23.5 × 16 cm. Blakiston Company, Philadelphia, Pa. 1945. Price, \$2.75.

During the hectic days of the induction centers, the neuro-psychiatrist's lot was a most difficult one. The Selective Service Act demanded a rapid evaluation of the men who ranged from believers in Mary Baker Eddy, the Mennonites, Jehovah's Witnesses, and the snake healers, through paranoid schizophrenics, organic encephalopathic states to malingerers. The psychiatrist's task in gauging the personalities of the heterogeneous group of men who had lived the relatively sheltered existence of home life and were then thrown into the tensions, anxieties, hostilities and prejudices of war, gave the authors a tremendous experience with this material which led to the excellent volume they have written.

Everyone is aware of the fact that war conditions, geography, climate, food and surroundings, induced neuropsychiatric responses for which there is no counterpart in civilian life. When natural anxiety at separation became complicated by any or all of these factors, the efficiency of thousands of young men was reduced. Actual combat conditions superimposed upon all of these alien sources of tension produced clinical pictures that tested the diagnostic acumen of many medical men who were confronted with myriads of complaints for which there was no organic basis.

The various methods by which the personality deals with anxiety are discussed. Psychosomatic visceral disturbances, depressions, conversion states, somatic regressions, concussion and exhaustion states, as well as malingering are elaborated upon. The psychiatric language is clear, readily understandable and the information factual. The authors relate their experiences in the use of somatic methods—such as pentothal interviews. One does not need to be a student of semantics to understand the text, and one welcomes the absence of such terms as eschatologic, ululation, ecdysiasm, so common in many psychiatric volumes.

This book is recommended for those who want to be informed about the psychological mechanisms of the war neuroses. The lessons learned are of use in civilian life. The neuropsychiatrist should be informed of the mechanisms and therapeutic approaches with which this little volume is replete. Many veterans have carried these neuroses as hangovers into civilian life. This volume will aid the neuropsychiatrist in accelerating their rehabilitation.

L. F.

Headache. By L. G. MOENCH, M.D. 207 pages; 21.5 × 14.5 cm. The Year Book Publishers, Inc., Chicago. 1947. Price, \$3.50.

This is an excellent and timely monograph on a very difficult clinical problem. The author has made an extensive survey of the literature and has arranged the material so that it is reasonably easy to read.

The first chapter deals with pain-sensitive structures of the head and the superficial localization of pain resulting from disturbances of these structures. There are numerous illustrations to clarify this relationship. This is the most interesting single feature of the book.

The other chapters concern headaches resulting from (1) intracranial lesions; (2) spinal puncture and ventriculography; (3) cranial nerve neuralgias; (4) headache of ocular origin; (5) headache of nasal origin; (6) headache arising from lesions in the neck; (7) headache from systemic disorders; (8) histamine headache; (9) migraine; and (10) headache of emotional origin.

Head pain is such a common occurrence and is associated with such a wide variety of illnesses that this book is of general interest. The author does not emphasize forcefully enough that the character and location of headache do not necessarily reveal the etiology of the discomfort and further that each case should be investigated thoroughly by history, examination and essential laboratory studies.

E. F. C.

Diseases of the Skin. 7th Ed. (Revised). By OLIVER S. ORMSBY, M.D., Rush Professor of Dermatology Emeritus, University of Illinois; and HAMILTON MONTGOMERY, M.D., M.S., Associate Professor of Dermatology and Syphilology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, Rochester, Minnesota. 1462 pages; 24.5 × 16 cm. 764 illustrations; 18 color plates. Lea and Febiger, Philadelphia. 1948. Price, \$18.00.

This outstanding text on dermatology, now in its seventh edition, is still probably the most all-inclusive general text on diseases of the skin in the English language.

The bibliography may be found at the bottom of each page and is so indexed that the student will have little trouble in finding the original source of the material presented. In the opinion of this reviewer this has a distinct advantage over those articles and texts in which the bibliography is included at the end of the article or chapter.

There is an excellent paragraph on histopathology included with each of the diseases. The chapter on mycology is well written and stresses the importance of a knowledge of mycology in the practice of dermatology.

The clinical descriptions of the various diseases have been written with such clarity that it would be almost impossible to misconstrue the authors' meaning. Careful perusal of this text fails to bring to light any useless material.

The chapter on syphilis has been revised and includes much of the late investigative work, particularly with reference to the use of penicillin.

It is the opinion of this reviewer that this text should be included in the library of every dermatologist and student of dermatology. It would prove to be an invaluable aid to the candidate for the American Board of Dermatology.

H. M. R., Jr.

Cancer: Diagnosis, Treatment and Prognosis. By LAUREN V. ACKERMAN, M.D., and JUAN A. DEL REGATO. 1115 pages; 25.8 × 18.5 cm. C. V. Mosby Co., St. Louis. 1947. Price, \$20.00.

This work deals mainly with cancer in the strict sense, but the authors have also included the more common neoplasms of connective tissue origin. The first five chapters give a very good review of our present knowledge of neoplasms, a summation of methods of treatment and an outline of past and present research. In the remaining chapters neoplasms are grouped by systems, each being discussed under the following headings: anatomy, incidence, pathology, clinical evolution, diagnosis, treatment and prognosis.

After a brief outline of the anatomy there is a discussion of lymphatic drainage which is accompanied by excellent anatomic charts. In the paragraph on incidence whenever possible the authors include factors which have a bearing on etiology. Both gross and microscopic pathology are presented, which together with an outline of the clinical evolution aid in reaching a tentative diagnosis. Under diagnosis are included various laboratory aids to be used, biopsy technics and differential diagnosis. The treatment of neoplasms is by no means uniform; for this reason all forms of therapy, in use at the better clinics, are given with a statement as to which are preferable. A most helpful addition to each section is a paragraph on prognosis. Each section has its own list of references. The book is well illustrated with good black and white pictures, but the color plates are disappointing in that the colors are not natural.

This work will be useful to medical students, who will find in one volume information gleaned from many sources. It is recommended to general practitioners and those who see cancer but do not treat it because it aids in early recognition, and because it tells what can be accomplished with present methods of therapy, thereby removing the entirely hopeless attitude which is still too prevalent. Lastly, those who specialize in the treatment of neoplasms will find this book a useful addition to their libraries.

A. G. S.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Biology of Disease. By ELI MOSCHCOWITZ, M.D., Physician, Mt. Sinai Hospital, New York, etc. 221 pp.; 26 × 17.5 cm. 1948. Grune & Stratton, New York. Price, \$4.50.

- Clinical Diagnosis by Laboratory Methods: A Working Manual of Clinical Pathology.* 11th Ed. By JAMES CAMPBELL TODD, Ph.B., M.D., Late Professor of Clinical Pathology, University of Colorado School of Medicine; ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, Mayo Foundation, University of Minnesota, etc. With the Collaboration of GEORGE GILES STILLWELL, A.B., M.D., Division of Clinical Laboratories, The Mayo Clinic. 954 pp.; 24 × 16.5 cm. 1948. W. B. Saunders Company, Philadelphia. Price, \$7.50.
- Clinical Endocrinology and Constitutional Medicine.* By A. P. CAWADIAS, O.B.E., M.D., F.R.C.P., Endocrinologist to the Order of St. John Clinic. 368 pp.; 25 × 16 cm. 1948. Frederick Muller, Ltd., London. Price, 42 shillings.
- Glomerular Nephritis: Diagnosis and Treatment.* By THOMAS ADDIS, M.D., F.R.C.P. (Edin.). 338 pp.; 24 × 16 cm. 1948. The Macmillan Company, New York. Price, \$8.00.
- Human Physiology.* 3rd Ed. By F. R. WINTON, M.D., D.Sc., Professor of Pharmacology, University College, London, and L. E. BAYLISS, Ph.D., Reader in Physiology, University College, London. 592 pp.; 24.5 × 16 cm. 1948. The Blakiston Company, Philadelphia. Price, \$7.00.
- The Natural History of Disease.* 2nd Ed. By JOHN A. RYLE, M.A., M.D., F.R.C.P., Professor of Social Medicine in the University of Oxford, etc. 484 pp.; 22.5 × 14.5 cm. 1948. Oxford University Press, New York. Price, \$7.50.
- Psychotherapy: Its Uses and Limitations.* By D. RHODES ALLISON, M.D., M.R.C.P., and R. G. GORDON, M.D., D.Sc., F.R.C.P. 160 pp.; 19 × 12.5 cm. 1948. Oxford University Press, New York. Price, \$3.00.
- Synopsis of Pediatrics.* 5th Ed. JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine, etc. Assisted by T. S. ZAHORSKY, B.S., M.D., Senior Instructor in Pediatrics, St. Louis University School of Medicine. 449 pp.; 20 × 13 cm. 1948. C. V. Mosby Company, St. Louis. Price, \$5.50.
- Taking the Cure: The Patient's Approach to Tuberculosis.* By ROBERT G. LOVELL, M.D., University Hospital, University of Michigan. 93 pp.; 19.5 × 13 cm. 1948. The Macmillan Company, New York. Price, \$2.00.

Erratum

In the April issue of the ANNALS, page 875, the receipt was acknowledged of "Textbook of Endocrinology" by Hans Selye, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada).

The price was given as \$10.24. The correct price is \$12.80.

COLLEGE NEWS NOTES

THE SAN FRANCISCO ANNUAL SESSION

The 29th Annual Session of The American College of Physicians, held at San Francisco April 19-23, 1948, under the Presidency of Dr. Hugh J. Morgan, Nashville, Tenn., and the joint Chairmanship of Dr. William J. Kerr and Dr. Ernest H. Falconer, both of San Francisco, goes into the archives of the College as one of the greatest and most outstanding meetings of the organization. Approval of both the scientific and social aspects of the meeting has been voiced universally. The gross registration was 3,374, of whom there were 997 members, 1036 guest physicians, 91 non-physician guests, 225 medical and/or graduate students, 537 exhibitors or their representatives and 488 visiting ladies. While the registration in San Francisco was considerably lower than at the 1946 Session in Philadelphia and the 1947 Session in Chicago (4037 and 4410, respectively), it was, nevertheless, gratifying to have so large a meeting on the West Coast. The San Francisco registration would have been greater except for the threatened coal strike, affecting transportation, and the fact that restriction in Canada of funds for travel in the United States prevented many Canadian physicians from attending the meeting.

The most significant papers on the program of General Sessions and Morning Lectures will be published in the *ANNALS OF INTERNAL MEDICINE*, probably starting with the July number. Non-member physicians who attended the Annual Session and paid a registration fee will receive the *ANNALS OF INTERNAL MEDICINE*, without charge, for one year beginning with the July number.

One hundred and four physicians were elected to Fellowship and 195 physicians were elected to Associateship. Names will be published elsewhere in these columns.

The Convocation was held on Wednesday evening, April 21, on which occasion the newly elected Fellows were inducted, President Hugh J. Morgan presented the Presidential Address and Dr. Alan Gregg, Director of the Medical Sciences of the Rockefeller Foundation, New York City, presented the Convocational Oration, "The Golden Gate of Medicine." Masterships in the College were conferred upon Dr. James Edgar Paullin, Atlanta, Dr. Maurice Charles Pincoffs, Baltimore, Dr. Anton Julius Carlson, Chicago, Dr. Henry Asbury Christian, Boston, and Dr. Oliver Hazard Perry Pepper, Philadelphia.

The John Phillips Memorial Medal for achievement in internal medicine for the year 1947-1948 was awarded to Dr. Ernest William Goodpasture, Professor of Pathology in the Vanderbilt University School of Medicine, Nashville, Tenn., with the citation, "His researches have helped to explain the behavior of ultramicroscopic germs of disease; his way of life has inspired to productive effort many generations of young physicians; as investigator and teacher combined, he has advanced the science of Clinical Medicine in perfect harmony with the objects of this College."

The James D. Bruce Memorial Medal for achievement in Preventive Medicine was awarded to Dr. James Stevens Simmons, Dean of Harvard School of Public Health, with the citation, "While Chief of Preventive Medicine Service in the Office of the Surgeon General, and Army Member of the President's Committee on Medical Research during the Second World War, his wisdom and judgment helped to save the lives of many soldiers. Now, as Army Officer turned Medical Educator, with soldierly forthrightness, he bids fair to advance the science of Public Health for the benefit of all our people."

The Alfred Stengel Memorial Award and Diploma were presented to Dr. Charles Ferdinand Martin, Emeritus Dean and Emeritus Professor of Medicine at the McGill University Faculty of Medicine, Fellow of the American College of Physicians since

1924, Master since 1929 and a Life Member; Past President and member of many of its important committees; a leader in the reorganization of the College, 1926-1929, with the citation, "He gave many years of loyal and devoted service to the College, exerted an outstanding influence on medical education, and contributed vastly to the practice of Internal Medicine and clinical research."

This marked the first occasion when the James D. Bruce Memorial Medal and the Alfred Stengel Memorial Award were conferred. They were both established through the generosity of the late Dr. James D. Bruce, former Vice President of the University of Michigan and former President of the College. The Alfred Stengel Memorial Award is primarily a service award in recognition of exceptional contributions to the American College of Physicians.

Also, during the Convocation ceremonies, announcement was made that the following physicians have been awarded Research Fellowships of the American College of Physicians for 1948-1949:

Dr. Charles Gordon Campbell
 Dr. Frank Herbert Gardner
 Dr. Samuel P. Martin
 Dr. Peritz Scheinberg
 Dr. Lutfu Lahut Uzman
 Dr. John Martin Weller

The Annual Banquet of the College on Thursday evening, April 22, commemorated, to a degree, the centennial anniversary of the "Gold Rush" which started in 1848. It was held in the Grand Ballroom of the Fairmont Hotel. Dr. William J. Kerr acted as Toastmaster and Dr. Frederick C. Woellner, Professor and Dean of the School of Education, University of California at Los Angeles, gave the address of the day, "A Philosophy of Trouble." A unique feature was the program with an illustration of the Harbor at San Francisco in 1848 and, inside the cover, a souvenir menu of the Eldorado Hotel at Hangtown, Calif., January, 1850, showing the bill of fare and prices so high as to dwarf presently accepted exorbitant rates.

The Ladies' Entertainment Committee conducted a program of entertainment for the visiting ladies, of exceeding interest and genuine pleasure. Local members in Northern California provided, as a special feature on the general entertainment program, a symphony concert by the San Francisco Symphony Orchestra, providing complimentary tickets to all members and their families in attendance.

At the Annual Business Meeting on Thursday, April 22, Dr. Walter W. Palmer, of New York, was inducted as President; Dr. Reginald Fitz, of Boston, was elected President-Elect; Dr. William S. Middleton, of Madison, First Vice President; Dr. Maurice C. Pincoffs, of Baltimore, Second Vice President; Dr. Charles E. Watts of Seattle, Third Vice President. Dr. Hugh J. Morgan, Nashville, Dr. Walter B. Martin, Norfolk, Dr. LeRoy H. Sloan, Chicago, Dr. George F. Strong, Vancouver, and Dr. M. A. Blankenhorn, Cincinnati, were elected to the Board of Regents for terms expiring 1951. Dr. George Morris Piersol and Dr. William D. Stroud, both of Philadelphia, were reelected Secretary-General and Treasurer, respectively, by the Board of Regents. Likewise, twenty-two state, provincial and territorial Governors were elected for terms expiring 1951, including:

E. Dice Lineberry, Birmingham.....ALABAMA
 Leslie R. Kober, Phoenix.....ARIZONA
 Lemuel C. McGee, Wilmington.....DELAWARE
 William C. Blake, Tampa.....FLORIDA
 Carter Smith, Atlanta.....GEORGIA
 Samuel M. Poindexter, Boise.....IDAHO

Walter L. Palmer (Chairman), Chicago.....	ILLINOIS (Northern)
J. Murray Kinsman, Louisville.....	KENTUCKY
Richard S. Hawkes, Portland.....	MAINE
Wetherbee Fort, Baltimore.....	MARYLAND
John G. Archer, Greenville.....	MISSISSIPPI
Harold W. Gregg, Butte.....	MONTANA and WYOMING
Robert O. Brown, Santa Fe.....	NEW MEXICO
Asa L. Lincoln, New York.....	NEW YORK (Eastern)
Charles A. Doan, Columbus.....	OHIO
Howard P. Lewis, Portland.....	OREGON
David W. Carter, Jr., Dallas.....	TEXAS
Karver L. Puestow, Madison.....	WISCONSIN
Rafael Rodriguez-Molina, San Juan.....	PUERTO RICO
John W. Scott, Edmonton.....	ALBERTA and BRITISH COLUMBIA
Charles H. A. Walton, Winnipeg.....	MANITOBA and SASKATCHEWAN
Leonard A. Scheele, Washington, D. C.....	U. S. PUBLIC HEALTH SERVICE

The report on the San Francisco Meeting would be quite incomplete without reference to a group of more than 200 members who traveled to San Francisco via a special train over the Baltimore & Ohio Railroad and the Atchison, Topeka & Santa Fe Railroad. The route of the train on the going journey from New York had to be altered due to restrictions of the Office of Defense Transportation because of the transportation emergency caused by the coal strike. However, special excursions on the going trip were made at Colorado Springs and Santa Fe, N. M.

At the end of the Session at San Francisco, the group spent a day in Yosemite Valley, two and one half days at Los Angeles, a day in the Grand Canyon of Arizona and a day at the Carlsbad Cavern of New Mexico. The Southern California members provided exceptional features of entertainment for the group while in Los Angeles, including a grand ball, high-lighted by movie celebrities, at the Los Angeles-Biltmore Hotel, sightseeing tours and visits to some of the various broadcasting programs. Many of the party were present at the last broadcast of Tom Brenneman's Breakfast Club in Hollywood, and two of the party won radios during the broadcast. (Mr. Brenneman died suddenly the following day, preceding his program.)

Entertainment features of the entire trip were planned with meticulous care and the trip was personally conducted by competent representatives of the participating railroads. The many commendatory letters received from those in the party attest to the exceptional pleasure all received.

THE AMERICAN COLLEGE OF PHYSICIANS TO CONVENE IN NEW YORK, 1949

The 30th Annual Session of the American College of Physicians will be held in the Waldorf-Astoria Hotel, New York City, March 28 through April 1, 1949, under the Presidency of Dr. Walter W. Palmer and the General Chairmanship of Dr. Franklin M. Hanger, Jr.

The 31st Annual Session will be held in Boston during the week of April 17, 1950. Increase in the number of large national conventions and continued pressure upon existing hotel and meeting room facilities have made it necessary for the College to work on a two-year in advance schedule. At the 1949 Annual Session in New York, the Board of Regents will select the 1951 meeting place, probably in the Mid-West.

A.C.P. POSTGRADUATE COURSES

Autumn 1948 Schedule

The general Postgraduate Bulletin covering autumn, 1948, courses offered by the American College of Physicians will be published early in July. It is anticipated that detailed outlines of courses will be available, likewise, at an early date. The fees for all courses are based on \$30 per week for members and \$60 per week for non-members with the provision that the College is obligated to accommodate its members first and to confirm registration of non-members not earlier than three weeks before the opening of a course, unless the registration clearly indicates adequate facilities for non-members. It is anticipated that there will be adequate facilities for some non-members in many of the courses.

List of Courses

CARDIOLOGY—National Institute of Cardiology, Mexico City; Ignacio Chavez, M.D., F.A.C.P., Director; two weeks, August 2–13; minimal registration, 25—maximal, 75.

This course represents a new and unique plan, offering a combined postgraduate course with a vacation provision. The class will meet from 9:00 a.m. to 1:00 p.m. daily, and each afternoon will be available for tours, inspection trips and entertainment. The faculty consists of outstanding authorities in Mexico, all of whom speak English, with one or more outstanding teachers from the United States. Dr. George R. Herrmann, Professor of Medicine at the University of Texas School of Medicine, will be one of the chief guest instructors and it is anticipated that Dr. Edward L. Bortz, Chairman of the College Advisory Committee on Postgraduate Courses, Philadelphia, will be present. The American profession knows too little about the important strides being made in this field in our neighboring Republic, and it is felt that this course will contribute much to the good professional relationships between the two countries. Mexico City is at such elevation that the climate is delightful and cool, even in the midst of summer. There is so much of interest and attraction that the vacation features alone should draw a large registration.

Full details will be furnished in the Postgraduate Bulletin concerning hotels, rates, and requirements for passports or visitors' permits.

Outline of Course

N.B. Each lecture will be of 30 minutes' duration, followed by 10 minutes allowed for questions and answers.

Monday, August 2.

A.M. Session.

9:00–9:40	Clinic Study of Rheumatic Carditis. Dr. I. Chavez.
9:45–11:30	Rounds to the Wards and Laboratories.
11:35–12:15	Radiological Signs of Mitral, Aortic and Mitral-aortic Lesions. Dr. N. Dorbecker.
12:20–1:00 P.M.	Rheumatic Fever—Special Aspects in Mexico—Clinical Picture. Pharmacology and Epidemiology. Dr. J. Carlos Gil.

Tuesday, August 3.

A.M. Session.

9:00- 9:40

The Diagnosis of the Common Congenital Heart Lesions.
Dr. G. Herrmann.

9:45-11:30

Rounds to the Wards and Laboratories.

11:35-12:15

Encephalic Lesions Responsible for Death of Patients with
Active Rheumatic Fever.

Dr. I. Costero.

12:20- 1:00 P.M.

Cardiac Lesions and Heart Diseases in Some Rheumatic Condi-
tions other than Rheumatic Fever.

Dr. J. Robles Gil.

Wednesday, August 4.

A.M. Session.

9:00- 9:40

Complete Heart-branch Block.

Dr. D. Sodi.

9:45-11:30

Rounds to the Wards and Laboratories.

11:35-12:30

Incomplete Heart-branch Block.

Dr. D. Sodi.

12:20- 1:00 P.M.

Bacteriological Studies in Subacute Bacterial Endocarditis.

Dr. M. Salazar Mallen.

Thursday, August 5.

A.M. Session.

9:00- 9:40

Differential Diagnosis between Constrictive Chronic Pericarditis
and Rheumatic Pericardial Symphysis.

Dr. I. Chavez.

9:45-11:30

Rounds to the Wards and Laboratories.

11:35-12:15

Clinical Diagnosis of Tricuspid Valve Disease.

Dr. S. Aceves.

12:30- 1:00 P.M.

Rest in Bed in Relation to Metabolism and Circulation.

Dr. F. de P. Miranda.

Friday, August 6.

A.M. Session.

9:00- 9:40

Some Differential Signs of Luetic Aortic Regurgitation.

Dr. T. O. Ramirez.

9:45-11:30

Rounds to the Wards and Laboratories.

11:35-12:15

Descending Syphilitic Myocarditis.

Dr. I. Costero.

12:20- 1:00 P.M.

Subacute Cor Pulmonale Following Acute Infectious Pulmonary
Processes.

Dr. R. Carral.

Monday, August 9.

A.M. Session

9:00- 9:40

Diet and Circulatory Diseases.

Dr. F. de P. Miranda.

9:45-11:30

Rounds to the Wards and Laboratories.

11:35-12:15

Some Physical Principles Underlying the Study of Circulation.

Dr. R. Limon.

12:20- 1:00 P.M.

Coronary Artery Heart Disease—Types and Management.

Dr. G. Herrmann.

Tuesday, August 10.

A.M. Session.

9:00- 9:40

Present Status of the Catheterization of the Heart in Congenital Heart Diseases.

Dr. R. Limon.

9:40-11:30

Rounds to the Wards and Laboratories.

11:35-12:15

The Problem of Auricular Flutter.

Dr. A. Rosenblueth.

12:30- 1:00 P.M.

Some Considerations about Intracavity Potentials in Men.

Dr. D. Sodi.

Wednesday, August 11.

A.M. Session.

9:00- 9:40

Surgical Treatment of Hypertensive Heart Disease.

Dr. L. Mendez.

9:45-11:30

Rounds to the Wards and Laboratories.

11:35-12:15

The Value of Angiocardiography in Heart Diagnosis.

Dr. N. Borbecker.

12:20- 1:00 P.M.

Tetralogy of Fallot and Anatomical Varieties with Similar Disturbances of Circulatory Dynamics; the Differential Diagnosis with Non-operable Conditions.

Dr. S. Novelo.

Thursday, August 12.

A.M. Session.

9:00- 9:40

Liver Impairment in Congestive Heart Failure.

Dr. B. Sepulveda.

9:45-11:30

Rounds to the Wards and Laboratories.

11:35-12:15

The Relation between the Chemical Structure and the Action of Digitalis-like Substances.

Dr. R. Mendez.

12:30- 1:00 P.M.

The Surgical Treatment of Congenital Heart Disease. The Necessity of Accurate Clinical Diagnosis.

Dr. S. Novelo.

Friday, August 13.

A.M. Session.

9:00- 9:40

Digitalis and Ouabain in the Treatment of Heart Failure.

Dr. I. Chavez.

9:45-11:30

Rounds to the Wards and Laboratories.

11:35-12:15

Present-day Concepts of the Mechanism and Treatment of Heart Failure.

Dr. G. Herrmann.

12:20- 1:00 P.M.

The Cardiac Patient and Aerial Transportation.

Dr. F. Mendoza.

INTERNAL MEDICINE WITH EMPHASIS ON PATHOLOGICAL PHYSIOLOGY—University of Cincinnati College of Medicine, Cincinnati, Ohio; M. A. Blankenhorn, M.D., F.A.C.P., Director; one week, September 13-18; minimal registration, 20—maximal, 40.

Last year Dr. Blankenhorn very successfully organized and directed a course for the College, INTERNAL MEDICINE WITH EMPHASIS ON METABOLISM AND NUTRITION.

The current course is new and in keeping with demands for courses associated with the basic sciences.

INTERNAL MEDICINE—University of Pittsburgh School of Medicine, Pittsburgh, Pa.; R. R. Snowden, M.D., F.A.C.P., Director; two weeks, September 20–October 2; maximal registration, 25.

This is a regular course on the College program, has been given successfully for several years and has been reported as being a valuable adjunct to preparation for Board examinations.

INTERNAL MEDICINE—University of Michigan Medical School, Ann Arbor, Mich.; Cyrus C. Sturgis, M.D., F.A.C.P., Director; two weeks, October 18–30.

This is a repetition of an outstanding course on the College program, a valuable one clinically and also for those preparing for Board examinations.

ENDOCRINOLOGY—Thorne Hall, Northwestern University, Lake Shore Dr. and Superior St., Chicago, Ill.; Willard O. Thompson, M.D., F.A.C.P., Director; one week; November 8–13; minimal registration, 50—maximal, 100.

Dr. Thompson has given this course on several previous occasions and it always was filled to capacity.

CARDIOLOGY—Emory University School of Medicine, Atlanta, Ga.; R. Bruce Logue, M.D., F.A.C.P., Director; one week, December 6–11; minimal registration, 30—maximal, 50.

Dr. Logue has previously successfully given a course in cardiology for the College, and this will be largely a repetition of that course.

GASTRO-ENTEROLOGY—Graduate Hospital of the University of Pennsylvania, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director; one week, December 6–11.

A repetition of one of the really fine and popular courses in this subject on the College schedule.

GASTRO-ENTEROLOGY—University of California and Stanford University Medical Schools, San Francisco, Calif.; Theodore L. Althausen, M.D., F.A.C.P., and Dwight L. Wilbur, M.D., F.A.C.P., Director; one week, dates yet to be announced.

This course is still in the planning at the time this announcement is prepared during early May. The Directors have been requested to arrange this course of one week's duration and to supply us dates and details. The final announcements will appear in the Postgraduate Bulletin. This course, if given, will be an outstanding one, directed by two great teachers on the West Coast.

RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE—Massachusetts General Hospital, Boston, Mass.; Paul D. White, M.D., F.A.C.P., Director; one week, dates yet to be announced; minimal registration, 70—maximal, 90.

This is the regular course in cardiology given for the College by Dr. White each autumn. It has always been oversubscribed and there is little hope of being able to accommodate any non-members in the course.

ADDITIONAL LIFE MEMBERS

The American College of Physicians takes great pleasure in reporting that under date of May 8, 1948, the following Fellows of the College became Life Members:

Dr. A. A. Sprong, Excelsior Springs, Mo.
Dr. Walter H. Wilson, Raleigh, N. C.
Dr. Olin S. Allen, Wilmington, Del.

DR. JAMES J. WARING BECOMES ASSOCIATE EDITOR OF THE ANNALS OF
INTERNAL MEDICINE

At their recent meeting in San Francisco, the Board of Regents elected James J. Waring, M.D., F.A.C.P., Denver, Colo., to succeed the late Dr. Gerald B. Webb as Associate Editor of the ANNALS OF INTERNAL MEDICINE. A Fellow of the American College of Physicians since 1928, Dr. Waring has long been active in its affairs having served in many capacities including those of Governor for Colorado, Vice President, and Regent. Dr. Waring has also been active as a teacher and investigator. He holds an appointment as Professor of Medicine in the University of Colorado School of Medicine and has served as Chairman of the Department of Medicine of that school, and as Chief of Medical Service of the Colorado General Hospital. Dr. Waring was also a Member and Chairman of the American Board of Internal Medicine and has given service to the Government as a Consultant to the Surgeons General and as a Member of Committees of the National Research Council.

Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., was elected President of the Association of American Physicians at its recent annual meeting at Atlantic City, N. J. Dr. Henry N. Thomas, Jr., F.A.C.P., Baltimore, was elected Secretary. The George M. Kober Medal was presented to Warfield T. Longcope, M.D., F.A.C.P., formerly of Baltimore. The address at the Association's dinner was delivered by O. H. Perry Pepper, M.A.C.P., Philadelphia.

ADMINISTRATIVE CHANGES, UNIVERSITY OF PENNSYLVANIA

The retirement on June 30 of Dr. A. Newton Richards as Vice President in charge of Medical Affairs was recently announced. Dr. Richards will be succeeded by R. C. Buerki, M.D., F.A.C.P., presently Dean of the University's Graduate School of Medicine and Director of the Hospital of the University of Pennsylvania and of the Graduate Hospital. Dr. William S. Parker, now Assistant Dean of the Graduate School of Medicine, will become the school's Dean on July 1.

In another change announced which will take place on the same date, Dr. John McK. Mitchell will succeed Dr. Isaac Starr as Dean of the University's School of Medicine.

A graduate of the University of Pennsylvania, Dr. Buerki served in the Army in World War I, subsequently engaged in medical practice and then achieved national recognition as an authority in hospital administration and in graduate medical education. Before returning to the University in 1941, he had served for a number of years as Superintendent of Hospitals, Executive Secretary to the Dean of the Medical School and Professor of Hospital Administration, in the University of Wisconsin. A charter fellow and former president of the American College of Hospital Administrators and a former president of the American Hospital Association and the Tri-State Hospital Assembly, Dr. Buerki was presented with the Award of Merit of the American Hospital Association in 1947.

On April 16, 1948, Brigadier General James Stevens Simmons, U.S.A. (Retired), Dean of the Harvard School of Public Health, was elected President of the Association of Schools of Public Health at the annual meeting of the Association held at the Connaught Laboratories, University of Toronto, Toronto, Canada.

Theodore G. Klumpp, M.D., F.A.C.P., President of Winthrop-Stearns Inc., was recently elected President of the American Pharmaceutical Manufacturers Association at the annual convention in Havana. Dr. Klumpp also is Chairman of the Board of Governors of the National Vitamin Foundation and Director of the American Foundation for Tropical Medicine.

Thomas Addis, M.D., F.A.C.P., Professor of Medicine Emeritus in the Stanford University, has been honored by the dedication to him of the current issue of the Stanford Medical Bulletin, entitled a "Festschrift for Thomas Addis." This issue contains appreciations of him by a number of his colleagues and 32 articles contributed by fellow workers in the field of kidney diseases and by associates and students.

Harold G. Trimble, M.D., F.A.C.P., Oakland, Calif., was a participant in the annual meeting on April 26, 1948, of the Ventura County Tuberculosis and Health Association as a speaker on the subject "Combined Operations—Target TB."

TESTIMONIAL DINNER GIVEN AT PHILADELPHIA FOR DR. EDWARD L. BORTZ

The medical profession of Philadelphia, aided by various and influential members of the laity, tendered to Dr. Edward L. Bortz, F.A.C.P., President of the American Medical Association, a testimonial dinner at the Bellevue-Stratford Hotel, at Philadelphia, on May 11. Dr. Theodore R. Fetter, President of the Philadelphia County Medical Society, was Chairman of the Committee on Arrangements; Dr. William Bates was Toastmaster. Greetings were extended on behalf of the College of Physicians of Philadelphia by Dr. J. Parsons Schaeffer, President; on behalf of The Philadelphia County Medical Society by Dr. Theodore R. Fetter, President, on behalf of the American College of Physicians by Dr. George Morris Piersol, Secretary-General. Addresses were made by Dr. Willard C. Rappleye, Dean of Columbia University College of Physicians and Surgeons, and by Rear Admiral Clifford Swanson (M.C.), U.S.N., Surgeon General of the United States Navy. A message and greetings were also extended by Colonel Otis Benson on behalf of the Air Surgeon of the United States Army. A medal of the City of Philadelphia was presented to Dr. Bortz.

J. C. Geiger, M.D., F.A.C.P., recently received from the French Government the Officer's Cross, Legion d'Honneur, with citation, "For distinguished public health services to France and in recognition of your untiring help to Frenchmen everywhere, particularly in San Francisco," and from the Argentine Government the Commander's Cross of the Heraldic Order del Libertador San Martin, with citation, "In recognition of your high merits in the field of public health."

WESTERN MICHIGAN REGIONAL MEETING

The spring meeting of the Western Michigan Members of the American College of Physicians was held at Battle Creek Country Club, May 19, 1948, under the Chairmanship of Dr. George W. Slagle, F.A.C.P., of Battle Creek.

Papers were presented by Dr. Manley J. Capron, F.A.C.P., "Newer Drugs in the Treatment of Asthma"; Dr. George A. Zindler (Associate), "Dermetallographism"; Dr. Arthur A. Humphrey, F.A.C.P., "Lipoid Pneumonia."

A social hour and dinner were held in the evening and Dr. Melvin Knisley of the University of Chicago was the guest speaker, showing a moving picture on "Sludged Blood."

Ralph Pemberton, M.D., F.A.C.P., Professor of Medicine in the Graduate School of Medicine of the University of Pennsylvania, was recently awarded an Honorary Doctorate in Medicine by the University of Montreal.

The Philadelphia County Medical Society held its annual Postgraduate Institute at Philadelphia, April 20-23, the central theme being "Symposia on Modern Methods of Diagnosis and Treatment." Numerous members of the College participated, including the following: Dr. Charles L. Brown, F.A.C.P., presiding over the Symposium on Common Blood Dyscrasias; Dr. Lowell A. Erf, F.A.C.P., "Present Status of Radioactive Substances and Nitrogen Mustard in Diseases of the Blood and Lymph Tissue"; Dr. Harry L. Bockus, F.A.C.P., "Cancer of the Gastro-Intestinal Tract. How Can the Early Diagnosis Be Made a Reality?"; Dr. Richard A. Kern, F.A.C.P., presiding over the Symposium on Newer Drugs and Procedures; Dr. Harrison Flippin, F.A.C.P., "Some Highlights in the Newer Treatment of Infections"; Dr. F. William Sunderman, F.A.C.P., "Protective Measures in Handling Radioactive Isotopes"; Dr. Thomas Fitz-Hugh, Jr., F.A.C.P., "The Newer Treatments in Hematology"; Dr. Hugh M. Miller, F.A.C.P., presiding over the Symposium on Problems of the Elderly Patient; Dr. Louis B. LaPlace, F.A.C.P., "The Aging Heart"; Dr. P. F. Lucchesi, F.A.C.P., "The Relationship of the Family Doctor to the District Health Units"; Dr. Rufus S. Reeves, F.A.C.P., "Preventive Medicine a Problem of Public Health"; Dr. Hobart A. Reimann, F.A.C.P., "Infectious Hepatitis and Homologous Serum Jaundice"; Dr. William P. Belk, F.A.C.P., "Evaluation of Laboratory Procedures in Jaundice."

The Centennial Meeting of the South Carolina Medical Association was held at Charleston, May 12-14, under the presidency of Olin B. Chamberlain, M.D., F.A.C.P., Charleston. Among the speakers were James E. Paullin, M.A.C.P., Atlanta; Warren W. Quillian, F.A.C.P., Coral Gables, Fla.; and Reginald Fitz, President-Elect of the College, Boston.

Henry W. F. Woltman, M.D., F.A.C.P., Rochester, Minn. and Irving S. Wright, M.D., F.A.C.P., New York, N. Y., were among the speakers at the annual meeting of the Illinois State Medical Society which was held in Chicago on May 10-12.

Mayo H. Soley, M.D., San Francisco, Calif., presently Professor of Medicine and Assistant Dean of the University of California Medical School has been appointed Dean of the University of Iowa College of Medicine and will assume that office on July 1, 1948.

The California Society of Allergy has been organized as the Allergy Section of the California Medical Association. Dr. George Piness, F.A.C.P., Los Angeles, and Dr. Albert H. Rowe, F.A.C.P., Oakland, were elected President and 1st Vice President, respectively. Dr. Frank G. Crandall, Jr., of Los Angeles, is the Secretary. The Society will hold meetings in conjunction with the annual meeting of the California Medical Association each year, and will conduct its scientific program and business meeting with the election of officers at that time. All physicians in California who are interested in allergy will be invited to attend the meetings.

Franklin H. Top, M.D., F.A.C.P., Detroit, Mich., was a speaker at the annual meeting of the Oklahoma State Medical Association, Oklahoma City, May 17-19, 1948.

The annual meeting of the American Association for the Study of Goiter was held in Toronto, Can., May 6-8, 1948, under the presidency of Dr. J. H. Means, F.A.C.P., Boston, Mass. Among the guest speakers were the following Fellows of the College: W. T. Salter, New Haven, Conn.; S. F. Haines, Rochester, Minn.; Earl M. Chapman and Elmer C. Bartels, Boston, Mass.; E. A. Sharp, Detroit, Mich.; and E. Perry McCullagh, Cleveland, Ohio.

With Anthony Bassler, M.D., F.A.C.P., New York, N. Y., as President, the National Gastro-enterological Association held its annual meeting in New York, N. Y., June 7-10, 1948. C. J. Tidmarsh, M.D., F.A.C.P., Montreal, Can., Vice President of the Association, was presiding officer. Among the Fellows who participated in the program as speakers were: Andrew B. Rivers, Rochester, Minn.; Richard B. Capps, Chicago, Ill.; Herbert T. Kelly, Philadelphia, Pa.; Burrill B. Crohn, Herman O. Mosenthal, Carl Muschenheim, Harold E. B. Pardee, New York, N. Y.; and Moses Paulson, Baltimore, Md.

The 14th annual meeting of the American College of Chest Physicians was held in Chicago, June 17-20, 1948. Papers were presented by George G. Ornstein, M.D., F.A.C.P., New York; Italo Volini, M.D., F.A.C.P., Chicago; Ben E. Goodrich, M.D., F.A.C.P., Detroit; and Maurice Segal, M.D., F.A.C.P., Boston. Andrew L. Banyai, M.D., F.A.C.P., Milwaukee, served as a Moderator and the following Fellows of the College presided at round table luncheons: Jay Arthur Myers, Minneapolis; Arnold S. Anderson, St. Petersburg, Fla.; Alvis E. Greer, Houston; Chauncey C. Maher, Chicago; Ben L. Brock, Downey, Ill.; C. Howard Marcy, Pittsburgh; Sumner Cohen, Oak Terrace, Minn.; Alvin L. Barach, New York; E. W. Hayes, Monrovia, Calif.; and J. Winthrop Peabody, Washington, D. C. H. C. Hinshaw, M.D., F.A.C.P., Rochester, Minn., and Chester S. Keefer, M.D., F.A.C.P., Boston were participants in a symposium on streptomycin.

ELECTIONS TO FELLOWSHIP AND ASSOCIATESHIP, APRIL 18, 1948

The Board of Regents of the American College of Physicians, meeting in San Francisco on April 18, 1948, elected 104 candidates to Fellowship in the College and 195 candidates to Associateship. The names of the new Fellows follow in CAPITAL LETTERS; those of new Associates in capital and lower case letters.

Crawford William Adams.....	Nashville, Tenn.
Sidney Louis Adelson.....	Detroit, Mich.
Melvin Louis Afremow.....	Chicago, Ill.
Howard Edwin Allen.....	Portland, Ore.
Leslie Robert Angus.....	Devon, Pa.
Robert Nerces Armen.....	Butler, Pa. (V.A.)
Charles Dorsey Armstrong.....	Menlo Park, Calif.
WILLIAM FRANCIS ASHE, JR.....	Cincinnati, Ohio
JOHN SPENCER ATWATER.....	Atlanta, Ga.
Louis Shattuck Baer.....	Burlingame, Calif.
RUSSEL LOBACH BAKER.....	Portland, Ore.
ROBERT SHERMAN BALDWIN.....	Marshfield, Wis.
William Mayo Balfour.....	Rochester, Minn.
Paul J. Bamberger.....	Bethlehem, Pa.
George Barton Barlow.....	Englewood, N. J.
A. Sidney Barritt, Jr.....	Brooklyn, N. Y.
Alexander George Bartlett.....	San Francisco, Calif.
George William Bascom.....	Toledo, Ohio

William Keller Beare.....	San Francisco, Calif.
Irving Addison Beck.....	Providence, R. I.
Robert Decker Beech.....	Salt Lake City, Utah
JAMES ROEDER BELL.....	Cleveland, Ohio
MORRIS BORIS BENDER.....	New York, N. Y.
Kenneth Louis Benfer.....	York, Pa.
Rudolph Berke.....	New York, N. Y.
Edward Bershof.....	Denver, Colo.
Robert Birchall.....	New Orleans, La.
Thomas Claiborne Black.....	Orlando, Fla.
Frank Wickes Blatchford, Jr.....	Winnetka, Ill.
Adolph Ebner Blatt.....	Indianapolis, Ind.
Virgil Henry F. Boeck.....	Buffalo, N. Y.
WILLIAM SCLAIR BOIKAN.....	Chicago, Ill.
George San Bozalis.....	North Little Rock, Ark. (V.A.)
Henry Dean Brainerd.....	San Francisco, Calif.
HARRY A. BRAY.....	Ray Brook, N. Y.
EDWARD ALBERT BRETHAUER, JR.....	Pittsburgh, Pa.
MORTON GOODWIN BROWN.....	Brighton, Mass. (V.A.)
Robert van Zandt Bucklin.....	Saginaw, Mich.
Edward Budnitz.....	Worcester, Mass.
PAUL HASKELL BURGERT.....	Lake Forest, Ill.
Edgar Murray Burns.....	Portland, Ore.
JOHN MARS CALDWELL, JR.....	M. C., U. S. Army
JAMES WILLIS CALLAWAY.....	La Jolla, Calif.
Sandy Baxter Carter, Jr.....	Atlanta, Ga.
William Robert Cate.....	Nashville, Tenn.
William Nesbitt Chambers.....	Hanover, N. H.
Henry A. Chapnick.....	Detroit, Mich.
Maurice R. Chassin.....	Maspeth, L. I., N. Y.
Paul Maxwell Clark.....	Denver, Colo.
Marshall Clinton, Jr.....	Buffalo, N. Y.
Max Cohen.....	Coatesville, Pa. (V.A.)
Lazarre John Cortright.....	San Francisco, Calif.
JOSEPH DAVID CROFT.....	Evanston, Ill.
John William Crosson.....	Philadelphia, Pa.
WILLIAM ROLAND CROWE, Jr.....	Atlanta, Ga.
Vernon Dale Cushing.....	Oklahoma City, Okla.
Edward Armstrong Custer.....	Peekskill, N. Y.
Donat Paul Cyr.....	Boston, Mass.
Allen Fitzhugh Delevett.....	Bridgeport, Conn.
Eugene Joseph Des Autels.....	Hines, Ill. (V.A.)
IRVING ISKOWITZ EDGAR.....	Detroit, Mich.
HERBERT EICHERT.....	Miami, Fla.
Samuel Elgart.....	Cincinnati, Ohio
IRVING LEONARD ERSHLER.....	Syracuse, N. Y.
Hugh Stewart Espey.....	Quincy, Ill.
NATHAN MILTON FENICHEL.....	Brooklyn, N. Y.
Louis David Fey.....	Seattle, Wash.
Sidney Morel Fierst.....	Brooklyn, N. Y.

Hyman Fisher.....	Sunmount, N. Y. (V.A.)
Louis James Fisher.....	La Canada, Calif.
GERALD FLAUM.....	New York, N. Y.
Joseph Clement Flynn.....	Tampa, Fla.
JOSEPH EUGENE FLYNN.....	New York, N. Y.
William Henry Flythe.....	High Point, N. C.
William Thomas Foley.....	New York, N. Y.
ELIOT EUGENE FOLTZ.....	Evanston, Ill.
Louis Michael Foltz.....	Louisville, Ky.
William J. Ford.....	Chicago, Ill.
Robert Ellison Lee Foster.....	Phoenix, Ariz.
WILLIAM BELL FOSTER.....	M. C., U. S. Army
Max S. Franklin.....	St. Louis, Mo.
ABRAHAM WALTER FREIREICH.....	Malverne, N. Y.
BENJAMIN DISRAELI FRIEDMAN.....	McKinney, Tex. (V.A.)
MAURICE HAROLD FRIEDMAN.....	Washington, D. C.
LEON JACOB GALINSKY.....	Des Moines, Iowa
David Gelfand.....	Philadelphia, Pa.
Victor Ginsberg.....	Brooklyn, N. Y.
Arthur Samuel Glushien.....	Pittsburgh, Pa. (V.A.)
HARRY GREGORY GOLAN.....	Richmond Hill, N. Y.
Seymour Goldgraben.....	Perry Point, Md. (V.A.)
Harold Isaac Goldman.....	Denver, Colo.
MARTIN GERHARD GOLDNER.....	Fort Logan, Colo. (V.A.)
DELMAR GOODE.....	Chicago, Ill. (V.A.)
Robert Archer Goodwin, Jr.....	Nashville, Tenn. (V.A.)
HERMON CAMP GORDINIER.....	Troy, N. Y.
Wendell Brown Gordon.....	Pittsburgh, Pa.
Milton Joseph Harold Grand.....	New York, N. Y.
Grant O. Graves.....	Columbus, Ohio
Joseph Greenblatt.....	Ottawa, Ont., Can.
Donald Wilfred Gressly.....	Rochester, Pa.
George Wainwright Griffin.....	Birmingham, Ala.
Gerard Patrick Joseph Griffin.....	Brooklyn, N. Y.
LEWIS GUNTHER.....	Beverly Hills, Calif.
Alf Torp Haerem.....	Redwood City, Calif.
Albert Berner Hagedorn.....	Rochester, Minn.
KENNETH ALEXANDER HAMILTON.....	Edmonton, Alta., Can.
H. PHILLIP HAMPTON.....	Tampa, Fla.
Harold Edward Hand.....	San Francisco, Calif.
Paul Scott Hansen.....	Santa Barbara, Calif.
JOSEPH EDWARDS JACKSON HARRIS.....	Albuquerque, N. M.
Thomas Anthony Harris.....	M. C., U. S. Navy
Thurston Harrison.....	Easton, Md.
Aubrey Biggs Harwell.....	Nashville, Tenn. (V.A.)
Francis Nelson Hatch.....	San Francisco, Calif.
Frederick Hamilton Hathaway.....	Lincoln, Nebr.
Frederick Carruthers Heal.....	Moose Jaw, Sask., Can.
Harry Hecker.....	Pawtucket, R. I.
GORDON EGAN HEIN.....	San Francisco, Calif. (V.A.)
THEODORE STANLEY HEINEKEN.....	Bloomfield, N. J.
Thurman Knight Hill.....	M.C., U. S. Army

SAMUEL J. HOFFMAN.....	Chicago, Ill.
Raymond Francis Holden, Jr.....	St. Louis, Mo.
RICHARD PHILIP HOWARD.....	Pocatello, Idaho
Patrick Connell Humphreys.....	Los Angeles, Calif.
HYMAN MORRIS HUREVITZ.....	Davenport, Iowa
SAMUEL HYMAN.....	Chicago, Ill.
Max Girtle Israels.....	Regina, Sask., Can.
Roger Alfred Jackson.....	Richmond, Va. (V.A.)
SAMUEL MAURICE JACOBSON.....	Cumberland, Md.
Harold Linton January.....	Albuquerque, N. M.
Frode Jensen.....	Denver, Colo.
Joseph Wilson Johnson, Jr.....	Chattanooga, Tenn.
RICHARD PAUL JOHNSON.....	M. C., U. S. Army
ROBERT MOORE JONES.....	Winnetka, Ill.
Benjamin Milton Kagan.....	Chicago, Ill.
James Roscoe Karns.....	Baltimore, Md.
Lester Karotkin.....	Houston, Tex.
KERMIT HARRY KATZ.....	Newton Center, Mass.
Gerald T. Kent.....	Cleveland, Ohio
Richard Nelson Kent.....	Fort Wayne, Ind.
John McCrae Kilgour.....	Winnipeg, Man., Can.
Wendell A. Killins.....	Green Bay, Wis.
ROBERT JOHN KINNEY.....	Topeka, Kans.
Albert David Kistin.....	Arlington, Va. (V.A.)
HUBERT DANIEL KITCHEN.....	Winnipeg, Man., Can.
ALVIN BERNT CLIFFORD KNUDSON.....	Washington, D. C. (V.A.)
Carl William Koerper.....	Oakland, Calif.
KENNETH GEORGE KOHLSTAEDT.....	Indianapolis, Ind.
Benjamin Osamu Kondo.....	Los Angeles, Calif.
Lawrence Melvin Kotner.....	St. Louis, Mo.
PHILIP KRAININ.....	New York, N. Y.
Louis J. Kroll.....	Baltimore, Md.
VICTOR HARRIS KUGEL.....	Miami Beach, Fla.
Carl William Kumpe.....	Covington, Ky.
JOHN HENDERSON LAMB.....	Oklahoma City, Okla.
Heinz Richard Landmann.....	Topeka, Kans. (V.A.)
JOHN SEWARD LAWRENCE.....	Los Angeles, Calif.
Joseph Davis Lea.....	Norfolk, Va.
RAYMOND ESSEX LEASE.....	Oyster Bay, N. Y.
Norman Benjamin Leet.....	Oakland, Calif.
GEORGE MARTIN LEIBY.....	Van Nuys, Calif. (V.A.)
Maurice Emanuel Leonard.....	San Francisco, Calif.
Franklin Earl Leslie.....	Baltimore, Md.
RICHARD LESSARD.....	Quebec, Can.
LOUIS EUGENE LIEDER.....	Cleveland, Ohio
MAX AUGUST LINDAUER.....	Philadelphia, Pa.
Harry Howard Lipcon.....	M. C., U. S. Navy
LEO WALTER LLOYD.....	Durango, Colo.
Walter Charles Lobitz, Jr.....	Hanover, N. H.
HAROLD WILLIAM LOVELL.....	New York, N. Y.

Moses Jacques Madonick.....	New York, N. Y.
Malcolm Judd Mann.....	Ithaca, N. Y.
Edward Wayne Marshall, Jr.....	Philadelphia, Pa.
Benjamin Franklin Martin.....	Winston-Salem, N. C.
RALF SAMUEL MARTIN.....	Portland, Maine
Oliver Shirley Matthews.....	Memphis, Tenn.
CARL LOUIS MAUSER.....	Oakland, Calif.
WALSH McDERMOTT.....	New York, N. Y.
John Charles McMillan, Jr.....	Oak Park, Ill.
Robert Monroe McMillan.....	Southern Pines, N. C.
JOHN PATRICK McVAY.....	Seattle, Wash.
Lester Meister.....	Beverly Hills, Calif.
MILTON MENDLOWITZ.....	New York, N. Y.
Urho Robert Merikangas.....	M. C., U. S. Army
Raymond Anthony Mezera.....	St. Louis, Mo.
CHRISTIAN FREDRIK MIDELFORT.....	La Crosse, Wis.
JOHN FLEEK MILLER.....	Newark, Ohio
John King Miller.....	Albany, N. Y.
SIDNEY MILLER.....	Birmingham, Mich.
William Bender Miller.....	Harrisburg, Pa.
C. SELBY MILLS.....	Phoenix, Ariz.
Nathan Mitchell.....	Brooklyn, N. Y.
William Edward Molle.....	Los Angeles, Calif.
Haywood Leland Moore.....	Brunswick, Ga.
Benjamin Gerald Morrison.....	Northampton, Mass. (V.A.)
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John Dibert Yeagley.....	York, Pa.
Donald Cook Young.....	Detroit, Mich.
Daniel Weston Zahn.....	Fort Logan, Colo. (V.A.)

OBITUARIES

DR. GEORGE McCCLAVE CULTRA

George McClave Cultra, M.D., F.A.A.P., F.A.C.P., passed away January 4, 1948, in Amarillo, Tex. Dr. Cultra had for several years suffered from a severe hypertension.

Dr. Cultra was born in Lincoln, Nebr., May 16, 1894. He graduated from the University of Nebraska College of Medicine in 1919 and served his internship at Kings County Hospital, Brooklyn, N. Y. He then spent two years in Alaska and, from 1922 to 1926, did general practice in the State of Washington. He came to Amarillo in 1926 and began the practice of Pediatrics, being one of the pioneers in this field in the Panhandle of Texas.

Dr. Cultra was certified by the American Board of Pediatrics in 1937 and was a Fellow of the American Academy of Pediatrics. He became a Fellow of the American College of Physicians in 1931.

Dr. Cultra continued in active practice until his death in spite of constant suffering. He was beloved by all who knew him. His sincerity, intellectual honesty and devotion to his patients' welfare truly represented the principles of the College. He was distinguished in appearance, reserved, and was blessed with a wonderful sense of humor. A constant student, he kept abreast of the advancements in his field. He took great pride in his membership in the College and will be sorely missed by his colleagues and patients.

W. CLAY DINE, JR., M.D., F.A.C.P.

DR WILLIAM LESTER SMITH

William Lester Smith, M.D., a Fellow of the American College of Physicians since 1931, died February 15, 1948. He had lived at Carbondale, Ill., after retiring from the United States Public Health Service in 1946.

Dr. Smith was born in Toledo, Ill., January 1, 1883. He received his A.B. degree from Austin College in 1901 and his M.D. degree from the University of Illinois College of Medicine in 1906. He was engaged in the private practice of medicine at Toledo, Ill., until he entered the Medical Service of the United States Army on the outbreak of war in the Spring of 1917. He was early assigned to the British Army in Flanders, where he distinguished himself by his energy and bravery. He was wounded in action and was awarded the British Military Cross, in addition to the Purple Heart. Following the War, he entered the United States Public Health Service and served in it until his retirement in 1946. He was Chief of the Medical Service of the U. S. Marine Hospitals in Norfolk, Va., Staten Island, N. Y., and New Orleans, La., and was Commanding Officer of the Public Service Hospital in Louisville, Ky.

He brought to his work in the Public Health Service the same energy and keen interest in the welfare of his fellow man that distinguished him as a private practitioner and as a soldier. With him each patient was an individual, deserving the best he had to give. Wherever he served, he elevated the quality of medicine around him, and inspired those under him with greater efforts on behalf of their patients. Those who knew him admired him for his ability and loved him as an individual.

WALTER B. MARTIN, M.D., F.A.C.P.

DR. GERALD B. WEBB

On the morning of January 27, 1948, Dr. Gerald B. Webb of Colorado Springs passed away following a heart attack. Thus came to an end a professional career of a man who had devoted his life to the study and treatment of tuberculosis.

Elected a Fellow of the American College of Physicians in 1928, Dr. Webb served it with distinction for many years, as Governor for Colorado from 1932 to 1938, Second Vice President in 1939-40, Regent from 1940 to 1943, and as Associate Editor of the Annals of Internal Medicine from 1934 until his death.

On August 27, 1938, the writer of this memorial notice had the honor of presenting Dr. Webb to President Norlin of the University of Colorado for the honorary degree of Doctor of Science. I quote from this citation:

"In the very year that Colorado Springs, largely through British capital, came officially into existence, Gerald Webb was born in England. Doubtless the budding Pike's Peak region was blissfully unconscious of the significance of the arrival of the infant Gerald, but it is a fact that each event was important for the other. The life of Gerald Webb was to become woven into the history of Colorado Springs.

"The head of a certain English school was a true prophet. Consulted about the mysterious disappearance of the Webb family cats, he predicted the boy Gerald would become a doctor, and so it proved. From 1890 to 1893 he studied medicine at the famous Guy's Hospital in London. As the spirit of William Osler hovers over Johns Hopkins Hospital and the influence of our Henry Sewall will always be felt at the University of Colorado Medical School and Hospitals, so the famous men of Guy's Hospital—Bright, Addison, Hodgkins, Gull and many others—inspire her students. His early training completed in these noble surroundings, Gerald came to Colorado. In 1896 he received the degree of Doctor of Medicine from the University of Denver, the medical department of which was later merged with the medical department of this University. There followed two years of study in London and Vienna. Guy's offered him a professorship in medicine but the appeal of Colorado was irresistible. He returned to Colorado Springs, for years the Mecca of the health-seeker, and has since devoted his life to the study and treatment of tuberculosis.

"He brought artificial pneumothorax from Rome; he showed that it was not necessary to use nitrogen gas in this life-saving procedure, that the air we breathe was more satisfactory, more convenient, just as safe. He made important contributions to our knowledge of resistance to tuberculosis. He gave scientific explanation for the beneficent effects of altitude and a dry climate in the treatment of this disease. He became President of the Climatological Association, President of the National Tuberculosis Association, a distinguished member of many other national organizations. During World War I he was Lt. Colonel in the United States Army and Senior Consultant in Tuberculosis to the American Expeditionary Force. He is the author of many scientific papers and addresses and several books, among them "A History of Tuberculosis." For years he drove from Colorado Springs to Denver to lecture at the Medical School on "The History of Medicine."

"With rare vision he early saw that in the treatment of disease, mind and body are inseparable. The curse of the long cure for tuberculosis is introspection, the remedy extrospection. Naturally endowed with a most winning personality and a scholarly mind, Dr. Webb has led his bed-ridden patients back to health along a delightful path of prescribed reading. In treating the body, he has not forgotten the spirit. Small wonder that in our medical world Colorado Springs has become synonymous with Gerald Webb."

During the last years of his life his interest in the birds, the insects, the flowers, the winter buds and all the little things of our natural environment intrigued him more and more. This interest was undoubtedly part of his English inheritance. His many friends East and West and across the water will miss him.

JAMES J. WARRING, M.D., F.A.C.P.

DR. FRANK BELL STEELE

Frank Bell Steele was born at Pinckneyville, Ill., on April 19, 1874. He attended Ohio Wesleyan University and the University of Tennessee, and received his M.D. degree from the University of Illinois College of Medicine in 1899.

Dr. Steele practiced medicine in Salt Lake City, Utah, for many years. He was affiliated with the Holy Cross Hospital there and was a member of the Salt Lake County and Utah State Medical Societies. Following several years of postgraduate study at the University of Chicago and in Chicago hospitals, Dr. Steele limited his practice to internal medicine.

In 1928 Dr. Steele entered the Veterans Administration and was assigned as an internist to the Veterans Administration Hospital in Hines, Ill. In 1934 he was assigned to the Veterans Administration Hospital in the Bronx, N. Y., and in 1941 to the Bay Pines, Fla., Hospital. He retired from the service in 1944 and lived thereafter in St. Petersburg, Fla., until his recent death.

Dr. Steele was a member of the old American Congress on Internal Medicine and a Fellow of the American College of Physicians since 1924.

COMMODORE FRANCIS W. F. WIEBER, (MC), USN

Francis William Ferdinand Wieber, M.D., F.A.C.P., was born in Plazfeld, Germany, April 5, 1861, and obtained his early education in that country. He attended the Long Island College Hospital and received his medical degree there in 1881. In 1886 he entered the Medical Corps of the U. S. Navy and served actively until his retirement in 1925. During his later years of service Dr. Wieber was Commanding Officer of the U. S. Naval Hospitals at Portsmouth, N. H., Fort Lyon, Colo., and San Diego, Calif. His contributions were recognized in the award of the Spanish Campaign Medal and the Victory Medal of World War I.

Commodore Wieber's death occurred on May 16, 1947. He had been a Fellow of the American College of Physicians since 1923.

DR. ALONZO HIGBEE WATERMAN

Dr. Alonzo Higbee Waterman died suddenly of a heart attack in his office in Chicago on November 26, 1947. Dr. Waterman was born in Minneapolis, Minn., on October 20, 1880. He attended both public and private schools there; he graduated from the Hahnemann Medical College and Hospital, Chicago, in 1906 and thereafter served as house physician at the Metropolitan Hospital, Department of Public Charities, New York, N. Y., 1906-1907. He attended the London Hospital in London, the Rotunda Hospital in Dublin, Queen Charlotte Hospital in Edinburgh, and also spent some time in both Paris and Rome in the years 1908-1910. He then began the practice of medicine in Chicago, becoming medical director of the Hotel Sherman Company, attending physician at the Henrotin Hospital, and consulting physician of the Illinois Masonic Hospital.

Dr. Waterman was a Diplomate of the American Board of Internal Medicine, a member of the Chicago and Illinois State Medical Societies, and, since 1924, a Fellow of the American College of Physicians.

He is survived by his widow, Henrietta Louise Janke Waterman, whom he married in 1906. Dr. Waterman possessed a very delightful personality and will be greatly missed by his many friends and patients.

WALTER L. PALMER, M.D., F.A.C.P.,
Governor for Northern Illinois

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